NITROUS OXIDE IN DENTISTRY

Nitrous Oxide in Dentistry

ITS DANGER AND ALTERNATIVES

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LLOYD-LUKE (MEDICAL BOOKS) LTD
49 NEWMAN STREET
LONDON
1960

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HAZELL WATSON AND VINEY LTD
AYLESBURY AND SLOUGH

PREFACE

EACH year, in England and Wales, about two and a half million administrations of general anaesthesia are given to ambulatory patients for extraction of teeth. To these must be added a large but unascertainable number given to ambulatory patients for minor operations of other kinds. It is probable in fact that, in the course of the year, administrations to ambulatory patients exceed in number those undertaken for the whole range of surgical procedures for which patients are admitted to hospital. Probably in at least three-quarters of the ambulatory patients the anaesthetic used is nitrous oxide. (The evidence on which these statements are based is given in Appendix E).

In the anaesthesia of ambulatory patients with nitrous oxide, it is common knowledge that oxygen is restricted and that there occur difficult administrations, which sometimes fail to provide satisfactory operating conditions. Doubt concerning the safety of restricting oxygen and dissatisfaction with the difficult administrations prompted me to investigate this field of anaesthesia, with special reference to dentistry, and to revalue the nitrous oxide method. My investigations and my study of alternative methods form the material of this monograph.*

The historical survey and general considerations, with which the monograph opens, confirmed my belief that restriction of oxygen and difficult administrations were related to one another, and that both were due to the low potency of nitrous oxide; moreover it seemed that the restriction of oxygen needed to overcome difficulties might on occasion be dangerous. It was desirable, therefore, to know how great and how frequent were the difficulties encountered in current practice.

This information I obtained by visiting dental extraction clinics in London. Observations made there showed that, even in the hands of experienced anaesthetists, difficulties were both frequent and considerable. It was probable, therefore, that difficulties would be still more in evidence in dentists' surgeries, where conditions were likely to be less favourable and the anaesthetists, as a rule, less experienced than in the clinics. If this were so, it seemed possible that oxygen might at times be restricted to an extent that endangered the brain.

This possibility I explored through a questionary to dentists; and

*A thesis accepted for the degree of Doctor of Medicine in the University of Cambridge.

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Mr. A. G. Prince (Case 18). For permission to use material previously published in *The Lancet*, I am indebted to the Editor, Dr. T. F. Fox. And for permission to use figures, I am indebted to General Armstrong and the Williams and Wilkins Company (Fig. 1), Professor S. S. Kety (Figs. 7, 11 and 12), the American Society of Anesthesiologists, Inc. (Figs. 11 and 12), Sandoz Limited, Switzerland (Fig. 7), and Dr. W. D. Wylie and Dr. H. C. Churchill-Davidson (Fig. 21). Finally, I wish to thank Mrs. Ann Durling and Miss Vivienne Hunt, who in turn gave me secretarial assistance.

J. G. BOURNE

March 1960

I got further information from other sources. The evidence I collected showed that severe disturbance of cerebral function was a not uncommon sequel of nitrous oxide anaesthesia in dentistry. Moreover, whilst not excluding the possibility that restriction of oxygen was partly to blame, the evidence brought to light an additional and unexpected hazard, which appeared to have been overlooked by dentists and dental anaesthetists. It suggested that the administration of nitrous oxide to patients in the dental chair was not infrequently associated with a common fainting attack. The effect of this in a patient anaesthetised sitting up might be severe stagnation or even complete cessation of cerebral blood flow.

A study of the circulation under dental gas was therefore made in the laboratory The results of the study supported my hypothesis: a record was obtained showing the onset of a fainting attack during an administration of gas.

The sequels of dental gas are discussed in the light of these findings. It was concluded that the main danger came from the upright position of the patient; but restriction of oxygen also was dangerous, as in fact it is acknowledged to be in all other fields of anaesthesia. A clinical study of the potency of nitrous oxide was therefore made to test the possibility of modifying the method by using nitrous oxide without restriction of oxygen. The results of this study showed that nitrous oxide was not potent enough to satisfy the requirements of anaesthesia in ambulatory patients; though some patients could be anaesthetised by it, others could not, and induction was too slow to be practicable.

The requirements and the possibility of satisfying them in other ways are therefore examined afresh. The suitability of cyclopropane is considered. And finally an account is given of the trial of cyclopropane in about 3,000 ambulatory patients

I wish to thank the dentists for their helpful co-operation. I am also grateful to Professor Alfred Meyer for examining the brain in Case 15, to Professor E. P. Sharpey-Schafer for making the blood-pressure recordings referred to in Chapter V, and to Dr. J. D. N. Hill for reporting on the electro-encephalograms in Case 18. I wish particularly to thank Dr. T. R. Malloy for providing me with case notes and follow-up reports on Case 17, and I am also grateful to Dr. K. Cameron, who kindly made available to me notes on this case from the Maudsley Hospital, London. For permission to publish cases I am indebted to Dr. W. H. Gabb (Case 1), Dr W. G. Tilleke and Dr. W. Whitelaw (Case 9), Dr. A. H. Saleh (Case 10), Dr. D. W. Livingstone (Case 11), Dr D. E. Price, Dr. A. B. Slack and Mr. J. J Wright (Case 14), Dr. D. M. Anderson and Dr. A. A. Miller (Case 15), Dr. V. K. Summers (Case 16), and Dr. G. E. Hyson and

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Chapter I

HISTORICAL SURVEY AND GENERAL CONSIDERATIONS

MOST of the work of anaesthetising ambulatory patients is done by general medical practitioners, dentists and junior hospital medical officers—'occasional' anaesthetists with but little training in anaesthesia. Their methods should be simple and effective and should have a wide margin of safety.

The nitrous oxide method, it is believed, meets the requirements and has stood the test of time. Minor operations, it is supposed, need only minor anaesthesia, and the low potency of nitrous oxide, the weakest of all anaesthetics, is thought to make it specially suitable for this work.

This is the traditional view, current today and upheld by authorities such as Macintosh and Bannister in the United Kingdom and Clement and Seldin in the United States of America. It is expounded by Macintosh and Bannister (1952*a*) as follows:

"The safeness of nitrous oxide is dependent upon its lack of potency. . . . nitrous oxide given with 20 per cent of oxygen will not only not cause death, but will scarcely produce unconsciousness." In contrast, more potent agents, they argue, can cause death even in the presence of a plentiful supply of oxygen. "To anaesthetise an average patient with nitrous oxide alone a certain amount of asphyxia must be deliberately induced; and, indeed, overdosage is nothing more nor less than an undesirable degree of asphyxia. The sight of a cyanosed and possibly jactitating patient is so alarming that it prevents even the inexperienced anaesthetist from being too venturesome with this anaesthetic."

Macintosh and Bannister acknowledge, however, that the low potency of nitrous oxide imposes limitations; that proper pre-anaesthetic medication and sometimes supplementary anaesthesia with thiopentone, hexobarbitone or ethyl chloride is necessary; and that successful administration depends largely on the experience and technical skill of the anaesthetist. "Nevertheless," they conclude, "nitrous oxide is quite suitable for almost all minor operations, and is the anaesthetic of choice for dental surgery in the ambulatory patient."

Clement (1951*a*) expresses his adherence to the traditional view

method were not disguised, and due regard was paid to its asphyxial element, its difficulties, dangers and complications—its disadvantages as well as its advantages. Here, also, were described techniques that have not since undergone any essential change and remain the basis of practice today.

Exclusion of Oxygen.—An outstanding feature of the method was exclusion of oxygen, the effect of which was at first mistaken for the action of the anaesthetic. In their preliminary report the Committee stressed, first and foremost, the need to exclude air. From animal experiments they found:

"1st. That the pure gas, so administered as to preclude the inhaling of any atmospheric air with it, *was* a powerful anaesthetic—more rapid in its action, although more evanescent in its effects, than chloroform and other anaesthetics then in general use;

"2nd. That if its administration were pushed beyond a certain point, it was capable of producing death; but

"3rd. That even when death appeared most imminent from its use, the allowing the animal to breathe fresh air, in most cases, brought it rapidly round."

For clinical use various kinds of apparatus were available. But whichever of these was selected, the Committee begged "to impress upon the administrator that it is absolutely necessary, for the production of the perfect anaesthetic effect of the gas, that it should be so constructed as entirely to prevent the inhalation of any atmospheric air during its administration."

In describing the conduct of anaesthesia the Committee might have been reporting present day practice, so little has the procedure changed. After a gag had been placed between the teeth to keep the jaws apart, the face-piece was applied and the administration of nitrous oxide was begun: "In from fifteen to twenty seconds the face may be expected to assume a dusky appearance; but the patient is usually conscious for from thirty to forty seconds. In about from forty-five to sixty seconds a further change may be expected to occur rather suddenly. The eyes lose their expression—move unequally, so as occasionally to cause squinting—and the pupil generally becomes somewhat dilated At this time the eyelids would contract if the conjunctiva were touched; but, if only one tooth is to be extracted, and that not a difficult one, the operation may be performed. If, however, several teeth have to be removed, the inhalation should be continued [for ten or fifteen seconds], although convulsive movements of the hands . . . may be expected to come on at this time. The pulse then becomes generally weaker, and the breathing stertorous, slower and intermitting. The inhalation must now be stopped immediately, and the extractions proceeded with. The pulse

thus: "Since nitrous oxide was first used by Horace Wells in 1844, it has been the anesthetic 'par excellence' in the dental field." He argues that "Its relative safety becomes evident when one considers its widespread use in the dental field (often in inexperienced hands) and the exceedingly small fatality rate that accompanies its use. Any anesthetic, such as N_2O, that has been in continuous and widespread use for over one hundred years must have certain attributes that more than compensate for its disadvantages. Otherwise, its use would have been abandoned long ago" (Clement 1951*b*). And Seldin (1947*a*) goes so far as to assert that "Only the inexpert question its efficacy, safety, and applicability in dental and oral surgery."

Early Observations

The method of obtaining with nitrous oxide brief anaesthesia for extraction of teeth began to be used in the United Kingdom in 1868. In that year, on March 31, Evans, an American dentist practising in Paris, brought the method to the notice of British dentists and anaesthetists by demonstrating it at the Dental Hospital in London.

The method was simple: nitrous oxide was administered, air being carefully excluded, until the patient became deeply unconscious, when the administration was stopped. During the short interval that elapsed before consciousness returned the extractions were made

Evans' demonstration was successful: eleven patients were treated and felt no pain. Onlookers were impressed by the speed of the effect and of recovery, and the method at once attracted attention. A committee was formed jointly by the Odontological Society of Great Britain and the Committee of Management of the Dental Hospital of London to inquire into the "value and advantages of the protoxide of nitrogen as an anaesthetic in surgical operations".

By December the Committee was ready with a preliminary report, based on eight months' experience and 1,380 administrations carefully watched and noted down by its members, and 1,051 reported to them by "practitioners of reliable authority." (*Transactions of the Odontological Society of Great Britain*, 1869).

This preliminary report, and the final one (*Transactions of the Odontological Society of Great Britain*, 1873), together with the discussions that followed their presentation and comments by other observers in contemporary journals, are of special interest. For the phenomena seen with this method of anaesthesia were then new and therefore keenly observed; and they were reported by minds that were fresh, not influenced by established doctrine, as, it seems, were those of some exponents of the method in later years, when it had become time-honoured. In the early reports the shortcomings of the

"Respecting the mode of action of the nitrous oxide," the annotation continued, "Dr. Richardson explained that it was not, in the true sense, the agent that caused the insensibility. . . . In fact, nitrous oxide is an asphyxiating agent. . . .

"In speaking out thus boldly to a professional audience, Dr. Richardson has not spoken a moment too soon. . . . Administration of nitrous oxide, or laughing gas, as it is commonly called, is becoming a pastime for amateurs" (*Lancet*, 1868*d*).

Apart from criticism by onlookers, however, the preliminary report itself contained in an appendix an account of "certain peculiar effects" which could not have been considered satisfactory. Of the 1,380 patients in whom anaesthesia had been observed by members of the Committee, five healthy males, not subject to fits, had severe epileptiform seizures during recovery after operation; in another patient the breathing suddenly stopped; in two others, faintness followed recovery; "Several hysterical women had slight fits of hysteria after taking the gas . . ."; and six patients "became greatly excited, and struggled so violently that the operations were performed with very great difficulty. . . ." Furthermore, in the discussion that followed presentation of the report, Cattlin (1869) described the behaviour of a 17-year-old girl, who, after brief anaesthesia for dental extraction, "remained in the operating-room for half-an-hour in a state of partial unconsciousness very like that produced by poisoning with opium." She was sent home in a carriage with attendants but continued for some time in a state of stupor. In another patient, an anaemic woman, the administration of nitrous oxide had to be cut short after two minutes on account of "faintness", which then lasted the whole day. And Kempton (1869) reported stupor lasting twenty minutes in a girl, aged 11. It is evident, therefore, that in its earliest days, serious drawbacks to the method had become apparent.

Today, it may seem remarkable that a method that produced in patients such alarming appearances and had such unsatisfactory features should have so quickly gained favour and passed into general use. Already, by 1873, in their final communication, the Committee were able to report no less than 58,000 administrations.

There were three reasons for the popularity of the method. First, The Chloroform Committee (1864), four years before Evans' demonstration, had published a report in which the danger with that agent, already coming to be regarded both by the medical profession and by the public with increasing anxiety, was amply confirmed. One hundred and twenty-three cases in which death could be positively assigned to its inhalation had been collected, and even that large number, the Committee suggested, was probably far short of the

and breathing should both be watched carefully at this stage of the administration, and, on the failing of either of them, air should be supplied."

From this description it is clear that in the opinion of the Committee, the margin of safety was narrow; respiratory arrest, in fact, had already been seen. It is not surprising, therefore, that the method was sharply criticised. Following a demonstration in which the gas had been successfully administered to one patient, the *Lancet* (1868*a*) reported: "In another case . . . the influence of the gas was not quite so satisfactory. The patient felt some pain. His appearance . . . was . . . that of a person in an epileptic fit, presenting as he did dense lividity of features, frothiness about the teeth, fixed and staring eyes with dilated pupils and rigid convulsions of the muscles of the arms. . . . It is impossible to imagine a condition of safety more strongly resembling that of imminent danger to life. . . ." On another occasion it was noted that "the patients all felt the extractions" and *afterwards complained of weakness, giddiness or faintness* (*Lancet*, 1868*b*); and following a demonstration at St. Bartholomew's Hospital, the *Lancet* (1868*c*) remarked that "in each of these cases the blood which flowed was very dark coloured . . . the pulse quickened and fell in force. . . . In the first case it 'went out' for thirty seconds . . . the breathing became abnormally quiet."

This report included an account of Clover's method of prolonging anaesthesia by giving air intermittently. "When the face had become perfectly purple, the pupils largely dilated, the conjunctiva insensitive, and the pulse nearly extinguished, Mr. Clover would remove his mask, the patient would breathe atmospheric air, and the reappearance of natural colour in the face after a few seconds became at once the sign of returning consciousness and the signal for the mask to be again applied. . . . One of the women was very hysterical after the operation, and the man made more noise and struggled more violently than we had previously noticed in any case. He had great muscular rigidity, and in all the cases we have seen there has been more or less tendency towards the same condition. In none has there been muscular relaxation." The report closed with the comment: "Useful where a single tooth has to be extracted, most persons would prefer taking chloroform had they to lose three."

More outspoken was the criticism of Dr. Richardson, president of the Medical Society of London, reported in an annotation in the *Lancet* entitled "The New Anaesthetic?". "The gas," he was reported as saying, "had been treated as an unknown, wonderful and perfectly harmless agent; whereas, in simple fact, it was one of the best known, least wonderful, and most dangerous of all the substances that had been applied for the production of general anaesthesia.

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real total of deaths caused by it. "At times, even with every care," the report ran, "and with the most exact dilution of the vapour, the state of insensibility may in a few moments pass into one of imminent death.

"It is therefore extremely desirable to obtain an anaesthetic agent which shall be capable of producing the requisite insensibility, and yet is not so dangerous in its operation as chloroform.

"Ether, to a certain extent, fulfills these conditions, but its odour is disagreeable, it is slow in its operation, and gives rise to greater excitement than chloroform. The Committee therefore concur in the general opinion which in this country has led to the disuse of ether as an inconvenient anaesthetic."

Next, there was the American experience. In their preliminary report the nitrous oxide committee mentioned the fact that a very large number of administrations of nitrous oxide, "now said to amount to upwards of 200,000 with the occurrence of but one death", had been given for dental extraction in that country. For, at the time of Evans' demonstration in London, the method had already been in use in America for five years Not unnaturally, this strongly influenced both the members of the Committee and others, particularly since Colton, who had initiated its use in America, "and who must undoubtedly be considered to have had the longest experience of its use of any man living", twice, in the summer of 1868, visited London, communicated "much valuable information" and gave several demonstrations.

Finally, the rapid induction of anaesthesia with nitrous oxide, and the rapid recovery from it, appealed to practical men "The rapid recovery was the most striking feature . . . a marked contrast to the length of time which so often elapses as the effects of chloroform pass off" (*Lancet*, 1868*b*).

It is understandable, therefore, that, in their final report, the nitrous oxide committee, although by then they had come to believe that the gas produced its effect by "preventing oxygenation of the blood", should have expressed the opinion that nitrous oxide was safer than any other anaesthetic yet discovered. For the only practicable alternative in those days was, in fact, chloroform, which, without doubt, would have caused more deaths.

Addition of Oxygen.—Nevertheless, the severe manifestations of oxygen lack with the method were objectionable. So, too, was the brevity of the resulting anaesthesia. To mitigate the former, the addition of oxygen in various proportions had been tried, but the results were unsatisfactory. The mixtures produced much struggling and excitement, with but imperfect anaesthesia (Coleman, 1873). It was not until the end of the century, following Hewitt's work, that

oxygen began to be used with nitrous oxide in the United Kingdom. Prolongation of anaesthesia had been obtained "by checking and re-supplying the gas through the face-piece", or nose-piece, if the operation was on the mouth—that is, by the method demonstrated by Clover. But prolongation by nasal administration, like the use of oxygen, was not revived until the end of the century.

These two innovations, the addition of oxygen and continuous administration by the nasal route for extraction of teeth (the only developments that distinguish modern practice from the original application of the method), while they improved the quality of anaesthesia and extended its duration when successfully applied, needed skill and experience. They took from the method one of the basic requirements—simplicity. The anaesthetist, who formerly had only to apply the face-piece and know how long the inhalation could be continued, now was called upon to judge precisely, from moment to moment, the amount of oxygen that was required. If he set the apparatus to deliver too little oxygen, convulsive movements occurred; if he gave too much, anaesthesia became too light. Very fine adjustment of the mixture was needed, and had to be made in advance of the patient's requirements. For, as Hewitt (1892) and later Macintosh and Bannister (1952*b*) pointed out, before such adjustments produce their effects there is a short interval during which anaesthesia continues to progress in the undesired direction.

"After some experience," wrote Hewitt (1897*a*), "the administrator will recognise that he had at his disposal an apparatus by which he can, if he wishes, obtain two totally different groups of symptoms.

"If very little or no oxygen be given, the ordinary phenomena of nitrous oxide narcosis will present themselves, viz., blueness, lividity, or duskiness of the features, epileptiform muscular twitchings of the trunk, extremities and face, and obstructive stertor.

"If too much oxygen be admitted, there will be no alteration in colour, no epileptiform convulsive movements, and no stertor, but violent mental and muscular excitement (laughter, shouting, kicking, stamping and struggling) will attend the administration, and will be almost as objectionable as the asphyxial phenomena produced by pure nitrous oxide . . .

"The anaesthetist has . . . to steer a middle course, and to keep a sharp look-out."

Restriction of Oxygen.—It must not be supposed, however, that, even in skilled hands, the use of oxygen with nitrous oxide removed from the method its hypoxic component. For, the middle course was successfully steered only when oxygen was restricted to proportions far below the 21 per cent of atmospheric air. Nor was this

restriction a merely passive consequence of the need to use nitrous oxide, because of its low potency, at the highest possible concentration. The restriction itself was required actively to contribute to the state of anaesthesia. In Clement's words: "The mild narcotic effect of nitrous oxide is enhanced by restriction of the oxygen intake" (Clement, 1951*c*); or, as Seldin (1947*b*) puts it: "Nitrous oxide produces anesthesia partly by limiting the oxygen supply to the brain. . . ." Macintosh and Bannister (1952*c*) go further and state that "in a robust patient *this deprivation of oxygen is often the main* factor in the resulting unconsciousness."

Today, no less than in 1868, during induction of anaesthesia with nitrous oxide up to the point where consciousness is lost, air is excluded and oxygen is usually withheld. Oxygen is then sparingly added. By Hewitt (1897*b*) it was given in the proportion of 2 per cent to 4 per cent and then progressively increased to 8 per cent or 9 per cent; McKesson used 4 or 5 per cent (McKesson, 1932); Clement uses 5 per cent: "From this point on", he writes, "the patient's reactions constitute the guide for adding more or less oxygen until the desired anesthetic level is reached" (Clement, 1951*d*). Macintosh and Bannister (1952*d*) recommend about 6 per cent. If nitrous oxide, they write, "mixed with enough oxygen to meet basal metabolic requirements, is administered to an average, fit patient who is unpremedicated, not only is it impossible to reach the point of death but it is often difficult to subdue him sufficiently to allow even a minor operation to be performed. This can easily be *verified in a patient who is to have a tooth extracted, by administer*ing nitrous oxide with, say, 12 per cent oxygen, and then allowing the dentist to begin. The great majority of normal patients in these circumstances will show considerable response to the stimulus. Some will scarcely lose consciousness and will give a vivid and unflattering account of the experience" (Macintosh and Bannister, 1952*e*).

In patients who are difficult to anaesthetise, the restriction of oxygen has to be even more severe. In such patients, states Clement (1951*e*), "The essentials for success during induction are pressure [of gas], the minimum of oxygen in the mixture, the time element and a disregard of cyanosis" McKesson (1920) commended the extraction specialist for not fearing cyanosis, and noted that this specialist "rarely removed the inhaler until his patient was fairly black. The fear of cyanosis by the surgeon and anesthetist," continued McKesson, "has been one of the most powerful influences in holding back the progress of nitrous oxide and oxygen."

Extreme measures have sometimes been taken by dental anaesthetists to curtail the oxygen supply to the brain in order to obtain

a satisfactory depth of anaesthesia with nitrous oxide. Macintosh and Bannister (1952*f*), for example, have recommended compression of the carotid arteries against the transverse processes of the cervical vertebrae, a procedure that they found "very helpful in increasing the effect of nitrous oxide in short operations when this gas alone was not adequate"; and McConnell (1948) relates how, in his in-experience, he applied a hand so firmly to exclude mouth breathing that he suffocated a patient to the point of respiratory arrest, so that artificial respiration had to be given.

The extent to which the customary exclusion of oxygen for some 50 seconds during induction of anaesthesia, followed by its restriction to small amounts, contributes to the state of anaesthesia, is indicated by certain observations entirely unconnected with anaesthesia. Haldane (1922), for example, in his study of respiration found that even with quiet breathing of an inert gas such as nitrogen, so that some time was needed to wash out the lungs, sudden and complete loss of consciousness was produced within 50 seconds. Again Humphry Davy in 1800, nearly half a century before the discovery of anaesthesia, recorded the fact that, when the inhalation of nitrous oxide was preceded by two inspirations of hydrogen, followed by a complete expiration, three inspirations of nitrous oxide were sufficient to deprive him of the power of standing so that he fell on his back (Davy, 1839). And in aviation medicine, as shown in Fig. 1, the altitudes that have been found to cause rapid impairment and loss of consciousness are physiologically equivalent to percentages of oxygen at sea level that correspond closely to those used with nitrous oxide in ambulatory patients.

The Margin of Safety with the Method.—From the foregoing it is apparent that, for the successful administration of nitrous oxide as used in ambulatory patients, oxygen has to be restricted to the narrow range that is critical for cerebral function. It would not be surprising, therefore, if the field of anaesthesia provided by the method was narrow and potentially dangerous, particularly with anaesthetists of limited experience. This, in fact, has been acknowledged by the very authorities who advocate the method. Clement writes: ". . . nitrous oxide-oxygen [anaesthesia] . . . may be very dangerous in the hands of the novice. The margin of anesthesia . . . is very narrow . . ." (Clement, 1951*f*). Seldin states: "The margin between the anesthetic and lethal concentration is very narrow in some patients. . . . The inexperienced and occasional anesthetist can readily carry his patient into sudden asphyxia . . ." (Seldin, 1947*c*). And Macintosh gives warning: "The snag is that in his efforts to tame a resistant patient by temporary extreme anoxia, the inexperienced anaesthetist can so easily overdo the 'softening up'

process, and inadvertently reduce his patient to respiratory arrest. And believe me, this is not to be risked lightly for the sake of a dental extraction in an alcoholic man with a flabby heart—particularly when the incident takes place in the dental surgery" (Macintosh, 1952).

It is not only the inexperienced anaesthetist, however, who may meet with this accident. Elsewhere, Macintosh has described its

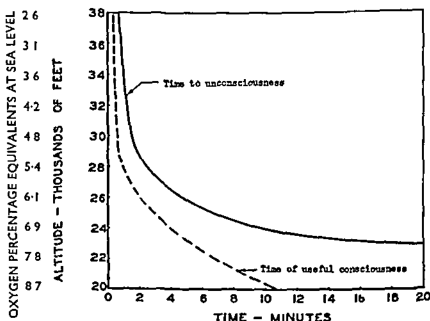


FIG 1.—Relationship of altitude to consciousness in healthy young airmen when suddenly deprived of their oxygen supply Continuous line indicates time to reach unconsciousness, broken line, time to lose a useful degree of consciousness. (Modified from Armstrong, 1952). *Left* Percentages of oxygen at sea level that are physiologically equivalent to the different altitudes. Mean of two sets of values. (*a*) when alveolar pCO_2 = 40 mm Hg (*b*) when alveolar pCO_2 = 10 mm. Hg (Horvath, *et al.* 1943).

occurrence at his own hands. The patient, a stout man of 50, had to be made very blue to get him under, whereupon his breathing suddenly stopped, the pupil became dilated and the eye death-like. Artificial respiration was ineffective until the patient had been lifted from the chair and placed on the floor (Macintosh and Bannister, 1952*g*). In McKesson's (1926) view every experienced dental anaesthetist had on occasion inadvertently carried deprivation of oxygen to dangerous extremes.

With a method in which the field of anaesthesia is so narrow, it is not surprising that a great deal of training and experience are needed

before it can be safely used, and that even then anaesthesia is not always satisfactory. Macintosh (1952) has expressed his doubt whether amongst the fully trained anaesthetists in this country there could be found a dozen who could give one hundred consecutive satisfactory administrations for dental extraction, whilst with 'occasional' anaesthetists the results, he believes, are still less satisfactory.

When all these facts are considered, it seems open to question whether the nitrous oxide method meets a single one of the three basic requirements that should be demanded of a method that is to be handled by the 'occasional' anaesthetist. Nitrous oxide began by being used in a way that had at least the merit of simplicity; but the method of using it today appears, in the light of this survey, to be neither simple nor effective nor to have a wide margin of safety. Yet, this is the agent that continues to be recommended as the anaesthetic of choice for the many thousands of 'occasional' anaesthetists, the rank and file into whose hands most of the work falls. Here, it seemed, was a contradiction that called for investigation. As a first step I studied current practice in dental extraction clinics.

Chapter II

OBSERVATIONS IN DENTAL EXTRACTION CLINICS

I OBSERVED 591 administrations of general anaesthesia in ambulatory patients for extraction of teeth—422 at London dental teaching hospitals and 169 at clinics of the London County Council (L.C.C.) School Dental Service.

As far as my observations were concerned, the patients were unselected Just over half (224) those at the teaching hospitals and all at the L.C.C. clinics were under 15 years of age.

The anaesthetic was given with the patient sitting up. The agent used was nitrous oxide, supplemented in about a third of the teaching hospital cases with trichloroethylene and in about a third of the L.C.C. clinic cases with ethyl chloride. The supplements were used only when induction of anaesthesia was troublesome, but not in all such cases.

The anaesthetists could be placed in five categories according to their status and experience:

Category A· Consultant anaesthetists each of whom had had at least fourteen years experience in dental clinics and had anaesthetised more than 10,000 dental patients.

Category B Senior registrar, registrar and senior house officer anaesthetists who worked in dental teaching hospitals and were therefore specially experienced in this work.

Category C· Undergraduate students supervised by the anaesthetists of Category A or B.

Category D A medical practitioner who was engaged in dental anaesthesia to the exclusion of all other work. He estimated that he had anaesthetised more than 20,000 dental patients.

Category E· General medical practitioners—'occasional' anaesthetists.

An attempt was made to classify the administrations according to the quality of the anaesthesia. As a rough measure of quality, note was taken of the amount of physical force that was needed to gain sufficient control over the patient for the extractions to be made On this basis, each administration was placed on completion in one of four classes referred to for convenience as good, moderate, poor and bad.

Class I (good): Little or no force needed.
Class II (moderate): Forceful control by one assistant.
Class III (poor): Forceful control by two assistants.
Class IV (bad): Forceful control by three or more assistants, or abandonment of the operation from failure to control the patient.

In addition, note was taken in each case of the presence or absence of cyanosis, hypoxic convulsive movements and stertor, and of serious complications.

Finally, the time taken by the dentist in making the extractions was measured in 312 of the teaching hospital cases and in all the L.C.C. clinic cases.

Results

Quality of Anaesthesia.—The distribution of the administrations by category of anaesthetist and class of anaesthesia is shown in Table I.

Table I shows that more than a third of the patients had to be firmly held during the administration and that, with every category of anaesthetist except D, in 10 per cent or more of the administrations anaesthesia was poor or bad. In three patients anaesthetised by consultant anaesthetists, anaesthesia completely failed and the operation had to be abandoned; and in another of their cases the extractions were made under great difficulties. Altogether, there were sixteen patients in whom anaesthesia was bad or failed: six men, six women, a youth and three children. In three of the men difficulty was expected; but there was nothing in the appearance of the others to suggest that they would be difficult to anaesthetise. In eight of the sixteen, supplements were used but seemed of little help.

Cyanosis.—Of the whole series of 591 patients, all except seventeen became cyanosed during anaesthesia. The combination of deep cyanosis, convulsive movements and stertor was common; it occurred in 21 per cent of the patients anaesthetised by consultant anaesthetists. Not infrequently, even with consultant anaesthetists, convulsive movements were severe and resulted in opisthotonos.

Complications

(*a*) *Syncope with respiratory arrest.*—Syncope with respiratory arrest occurred in two patients, a boy aged 5 anaesthetised by a consultant anaesthetist, and a girl aged 8 anaesthetised by a general medical practitioner. In each patient the syncope occurred during a difficult induction with unsupplemented nitrous oxide.

In the boy the mouth prop, which had been placed between the teeth before the administration was started, slipped and the jaws

TABLE 1

DISTRIBUTION OF THE ADMINISTRATIONS BY CATEGORY OF ANAESTHETIST AND CLASS OF ANAESTHESIA.

	Category of Anaesthetist	*Number of Administrations* — *By Class of Anaesthesia* 1 (*Good*)	2 (*Moderate*)	3 (*Poor*)	4 (*Bad*)	*Total in Category*	*Percentage in Classes 3 and 4*
Teaching Hospitals	A (Consultants)	104	30	14	4	152	12%
	B (Sen. Reg.; Reg.; Sen. House Officers)	143	54	23	9	229	14%
	C (Students)	17	20	3	1	41	10%
L.C.C. Clinics	D (Whole-time Dental Anaesthetist)	67	27	6	0	100	6%
	E (Gen. Med Pract.)	32	28	7	2	69	13%
	Total	363 (61%)	159 (27%)	53 (9%)	16 (3%)	591	12%

became clenched. While an attempt was being made to prise open the mouth he started to regain consciousness and cry. Nitrous oxide was therefore given again, as at the beginning, without oxygen; but after a few breaths he became deathly pale and limp, and stopped breathing.

The girl struggled during induction. After about a minute, struggling gave place, without any intervening pause, to the convulsive movements of hypoxia. The change in character of the movements appeared to escape the notice of the anaesthetist, who continued to withhold oxygen in an attempt to control the patient; but almost at once this patient, also, became deathly pale and limp, and stopped breathing. Both patients started breathing again after being given oxygen and artificial respiration for about a minute.

(*b*) *Delayed Recovery of Consciousness.*—This was seen in one patient, the boy who had syncope and respiratory arrest. When spontaneous respiration had returned, the extractions were made and he was left sitting in the chair to recover from the anaesthetic. Three and a half minutes later he was carried unconscious to his mother in the recovery room. He was still unconscious fourteen minutes later, when he was carried away by his mother, who seemed unaware of the fact that his condition was unusual. The case was not followed up.

Time Needed for Extractions.—The time taken by the dentist in making the extractions was less than a minute and a half in two-thirds of the teaching hospital cases, and did not exceed one minute in any of the L.C.C. clinic cases.

COMMENT

These observations showed that even in the most experienced hands difficulties with the nitrous oxide method were both frequent and considerable. Struggling was common, and to control the patient the anaesthetist had to rely mainly on restriction of oxygen, the supplements seeming to be of little help. Restriction of oxygen, however, did not always bring success and sometimes led to convulsive movements, which themselves were troublesome. The failure of the anaesthetist, in one instance, to notice the transition from struggling to hypoxic convulsions, with the result that oxygen was withheld, when, in fact, it was urgently needed, was a mistake that McKesson (1926) stated was common.

The fact that in this small series there were two cases of syncope with respiratory arrest, recovery of consciousness being delayed in one of the patients, strengthened my belief that the margin of safety was narrow with this form of anaesthesia, and that the method might be dangerous in the hands of the 'occasional' anaesthetist.

The traditional view that the method was one of proven safety was, perhaps, based on the immediate mortality in the chair and did not take into account the possibility of hypoxic cerebral damage, with its delayed manifestations. If this was a risk in the clinics, as my observations suggested, it might be a still greater danger in dentists' surgeries, where the anaesthetists were probably less experienced and the conditions less favourable than in the clinics. To investigate *this possibility I sought information from dentists.*

Chapter III

SEQUELS OF NITROUS OXIDE IN DENTISTRY: INFORMATION FROM DENTISTS

I SENT a questionary (Appendix D) to a random sample of 386 dentists in the United Kingdom. The sample was formed by selecting the first dentist listed on each page of the current Dentists Register, an alphabetical list containing the names of 15,267 dentists living in the United Kingdom and 426 dentists living abroad, whom I excluded.

The main question (Question 6) in the questionary was:

"*Have you ever known a patient who did not immediately regain consciousness after gas but remained unconscious or stuporous for half an hour or more?*"

Replies to the questionary were received from 345 dentists—89 per cent of those to whom it was sent. Sixty-two of those who replied indicated by their answer to Question 1 that they did not use gas or any form of general anaesthesia for patients in the dental chair. They therefore left Question 6 and the other questions unanswered. Of the remaining 283 who replied, all of whom used gas, 107 answered 'yes' to Question 6. This number represents 31 per cent of all who replied to the questionary, or 38 per cent of those who used general anaesthesia.

These results are summarised in Figs. 2 and 3, in which the dentists are grouped according to their year of qualification. In each figure the column on the left, marked Dentists Act, 1921, represents dentists holding no qualifying diploma; they entered practice before 1921, but the year is not stated in the register.

Before these replies could be interpreted as representing roughly the general experience of dentists throughout the United Kingdom, it was necessary to exclude bias in the group of dentists who did not reply to the questionary and to confirm the answers given to Question 6.

To test the possibility of bias in dentists not replying to the questionary, I selected by drawing lots fifteen of those who had not replied by a certain date, when nearly all the replies had been received

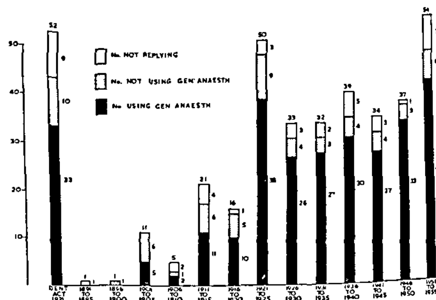


FIG. 2.—Dentists to whom questionary was sent, grouped by year of qualification. Total height of each column represents number (top of column) to whom it was sent At side of column· number not replying, number not using, and number using, general anaesthesia.

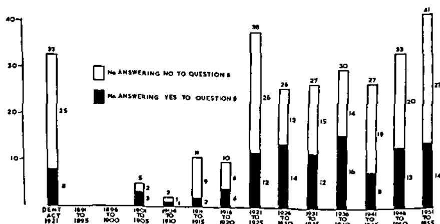


FIG. 3.—Dentists using general anaesthesia, grouped by year of qualification Total height of each column represents number (top of column) using it. At side of column: number answering 'no' and number answering 'yes' to Question 6,

and no more were coming in, and, by making a special appeal, obtained replies from twelve of them: nine used general anaesthesia and six answered 'yes' to Question 6. (Since these replies did not differ significantly from those already received, they have been included in the results given above.)

I was able to get in touch with 99 of the 107 dentists who had answered 'yes' to Question 6. All of them confirmed their answer and could recall, on an average, at least three cases each. I then selected by drawing lots fifteen of the 176 dentists who had answered 'no' to this question. Five of the fifteen, on being interrogated at once corrected their answer to 'yes' and described cases they had seen. The first dentist said that he would never forget his case; he thought the patient, a man of 55, was dead. He was unconscious about an hour. The second dentist said that, in the previous year, one of his patients, a former heavyweight boxer, was still unconscious an hour after being given gas, when the ambulance came to take him to hospital. He had seen several cases. The third dentist also had seen several cases. One patient, a hospital secretary, was stuporous for six hours and had to be admitted to hospital. The fourth dentist described the case of a powerful, alcoholic man, whom he himself had anaesthetised. The patient was unconscious for twenty minutes and then stuporous for two or three hours. He did not fully recover for two or three days. The fifth dentist had seen three cases during his ten years in practice. Each had been unconscious nearly an hour. He had answered 'no', he explained, because the cases had occurred with general medical practitioner anaesthetists, and no case had occurred since he had taken to using only a skilled anaesthetist.

These corrections suggested that in reality more dentists in my survey had seen cases of delayed recovery than had acknowledged having done so by answering 'yes' to Question 6. It seemed fairly certain that, in round numbers, at least one third had met with the condition, and had seen, on an average, not less than three cases each. If this were true of the whole population of dentists in the United Kingdom it would mean that about 15,000 cases had been seen in the life experience of existing dentists. Assuming a mean experience of 30 years, it would seem that cases were occurring in dental practice in the United Kingdom at the rate of 500 a year.

The 99 dentists who answered 'yes' to Question 6 and with whom I was able to get in touch, each described to me the case that stood out most clearly in his memory, and sometimes I was able to get further information from the anaesthetist.

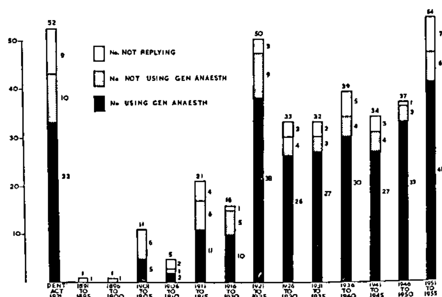


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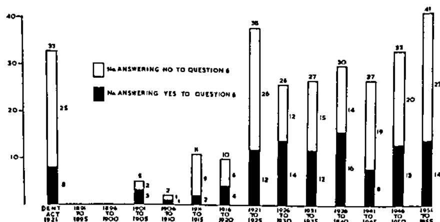


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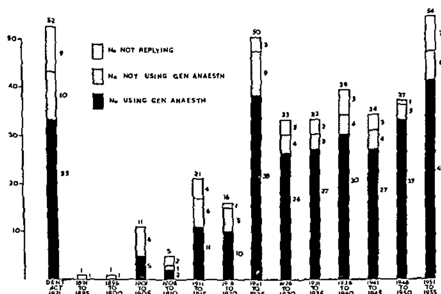


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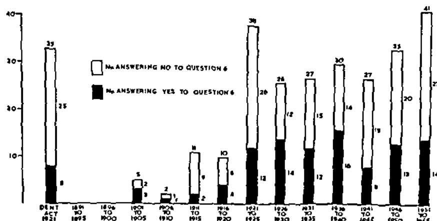


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Illustrative Cases

Case 1.*—A healthy girl of nearly 5 years was given gas for the extraction of one tooth She was shy but docile and did not seem frightened; and she took the gas smoothly, without difficulty or cyanosis. During the administration she slid down in the chair and was pulled up by the head. The tooth was quickly extracted. "She appeared to begin to regain consciousness and I think smiled and phonated, but then she became apparently 'shocked', sweaty and pale, and I thought was about to vomit. However, she slipped back into unconsciousness and the pulse became imperceptible. She was given oxygen and nikethamide ('Coramine') injections, and after about half an hour she appeared to be less deeply unconscious and the pulse improved. There were no localising signs of cerebral damage and there was no neck rigidity, but some teeth-grinding."

She was still unconscious eighteen to twenty-four hours later, when she was admitted to hospital. The cerebrospinal fluid was normal. There was low-grade irregular fever, which lasted several weeks. She was without reflexes until the seventh day, when the knee-jerks were obtained. The left plantar response was extensor. She remained unconscious nearly two weeks, after which she was imbecilic in appearance, giggling continuously, and was incontinent. Six weeks after the gas she was feeding herself a little, but was still imbecilic and incontinent. She then began to recover, and four months after the gas she appeared to have recovered completely.

She was re-examined at the age of 9 and no abnormality was found. She had normal physical activity, and mentally was only slightly behind her contemporaries. Her only symptom was occasional nocturnal enuresis

Case 2.—A pale woman of 28 was given gas for the extraction of one tooth. She did not seem nervous and took the gas well. As the dentist picked up the forceps to make the extraction her face became grey. He quickly extracted the tooth, the gas was stopped, and she was left sitting in the chair to recover. Her pallor was now extreme and she was sweating profusely. Her pulse was slow and difficult to feel. After about five minutes, being still unconscious, she was carried from the chair to a couch in the recovery room For more than half an hour she remained deeply unconscious, and after a further hour was stuporous and able only to stagger. She had to be assisted downstairs and sent home in a taxi.

Her pallor and sweating, and especially the slowness of her pulse, strongly suggested to me that she had fainted during the

* For the report on this case I am indebted to the anaesthetist, Dr. W. H Gabb, a physician experienced in giving gas for dental extraction

administration of gas. When I put this to the dentist he agreed that the signs were suggestive, but thought the condition was "too severe" for fainting.

Case 3.—A nurse aged 24 was given gas for the extraction of five teeth. When three of the teeth had been extracted she suddenly became grey and pulseless and stopped breathing. "The heart stopped beating for a minute or two," the dentist said, "and I thought she was dead." The chair was tilted backwards and she was given artificial respiration and oxygen. After about three minutes, breathing and feeble heart beats returned. She remained unconscious half an hour and then stuporous two hours, after which she recovered. It was later found that she had previously had a similar reaction to gas.

Case 4.—A man of 27, who looked pale and delicate, was given gas and trichloroethylene ('Trilene') for the extraction of one tooth. He became a little cyanosed and then suddenly turned slate grey. "The whites of his eyes turned up and I thought he was a goner," the dentist said. The pulse was feeble and very slow, there was profuse sweating, and twitching of muscles, mainly in the legs. He was unconscious half an hour and then dazed for twenty minutes. When he had recovered he told the dentist that he had had a similar reaction before with gas, and also on another occasion when he had had a tooth extracted under local anaesthesia.

Case 5.—A woman of 25 was given gas for the extraction of five teeth The administration was "uneventful, but the patient refused to come round. Her breathing was normal, but her behaviour was very abnormal, being more that of a gross mental defective, her face, mouth, and tongue making the most amazing contortions. She was quite unconscious of her surroundings and made no noise. Talking to her, exhortations, and slapping were of no avail. She remained in this state for one and a half hours and then, quite suddenly, became almost normal. She has no recollection of the affair."

Case 6.—A strapping 18-year-old girl was given gas at a dental teaching hospital for the removal of a few teeth. Her behaviour afterwards was as follows: "Instead of recovering normally she went into hysterical convulsions, each lasting about a minute, followed by about five minutes of what appeared normal sleep. During the attacks it took the combined efforts of myself, anaesthetist, sister, nurse, and two students to restrain her. It was about two hours before she recovered sufficiently to leave."

Case 7.—A Naval petty officer, aged 35, a boxer, was given gas for the extraction of one tooth. Previously, the dentist had tried to anaesthetise him with nitrous oxide but had failed. This time, therefore, a trained anaesthetist was asked to give the gas. The

dentist noticed that the anaesthetist "had to get him black in the face to get him under", whereupon respiration suddenly ceased. He was placed on the floor where he lay motionless for about five minutes. This was followed by maniacal outbursts of great violence. "He wrecked the place," the dentist said, "and it took five of us to hold him down." For more than half an hour he was completely unconscious, and for a further hour or more he was stuporous. Next day he had recovered.

Delayed Recovery of Consciousness

The proportion of cases in which recovery of consciousness was delayed half an hour or more varied surprisingly in the practices of different dentists. Some dentists assured me that in a long experience with thousands of gas cases they had never seen the condition. In the practices of other dentists it was almost common. They made such estimates as: 1 case a year, 6 cases a year, 1 case a month, 1 in 200 gas cases, and even 1 in 100 gas cases.

One dentist met the condition so often that he had been obliged to furnish a recovery room into which patients could be carried. His practice was in an industrial area and he observed delayed recovery mainly in men between their late twenties and early forties, exhausted by heavy work in factories.

It was surprising also, as shown in Fig. 3, that, of 74 young dentists in my survey, who had been in practice less than ten years, over a third had seen the condition, and most of them more than once, whereas of 99 dentists who had been in practice more than 30 years, less than a third had seen it. From this it seemed that the condition was becoming more common, although there were other possible interpretations.

The distribution, by year of qualification and number of cases seen, of the 99 dentists who gave descriptions of cases is shown in Table II; and in Table III the cases are analysed.

Analysis of the 99 cases suggested the following broad generalisations:

The condition was seen in men and women, often young, and in children; in many cases, three teeth or less were to be extracted; pre-anaesthetic medication had rarely been given; it happened with specialist as well as with less experienced anaesthetists, and at teaching hospitals as well as in dentists' surgeries; all the well known makes of anaesthesia apparatus were implicated.

Symptoms and Signs.—Deathly pallor, sometimes preceded by cyanosis and sometimes associated with profuse sweating, was a common and striking feature. The pulse was remarked on in few cases; in most it was slow and weak, and in the remainder, absent. In

TABLE II

DISTRIBUTION BY YEAR OF QUALIFICATION AND NUMBER OF CASES SEEN OF THE 99 DENTISTS WHO GAVE DESCRIPTIONS OF CASES

Year of Qualification	*Number of Dentists*							
	By number of cases seen							*Total*
	1	2	3	4	5	6	*More than* 6	
1951–1955	9	2	2	1				14
1946–1950	3	1	3			3	3	13
1941–1945	2	2	2	1			1	8
1936–1940	8	5					3	16
1931–1935	3	4	2				1	10
1926–1930	3	2	2		1	2	1	11
1921–1925	3	4			1		4	12
1916–1920		1				1	2	4
1911–1915	1						1	2
1906–1910	1							1
1901–1905	1							1
Dentists Act 1921		4	1	2				7
Totals	34	25	12	4	2	6	16	99

TABLE III

ANALYSIS OF 99 CASES OF DELAYED RECOVERY

Observation	*Number of cases in which observation was reported*	*Total*
PLACE OF OCCURRENCE:		
Dentist's surgery	75	
Hospital or clinic	9	92
Dental teaching hospital	8	
AGE OF PATIENT (Years):		
Under 15	26	
15–20	10	96
21–40	37	
Over 40	23	
SEX OF PATIENT:		
Male	27	
Female	59	86
NUMBER OF TEETH EXTRACTED:		
1–3	33	
4–6	17	70
More than 6	20	
PRE-ANAESTHETIC MEDICATION:		
Given	6	74
Not given	68	
ANAESTHETIST:		
Dentist making extractions	17	
Another dentist	13	79
General medical practitioner	39	
Specialist anaesthetist	10	
ANAESTHESIA MACHINE:		
'Walton'	27	
'McKesson'	13	47
'Jectaflow'	3	
Other	4	

TABLE III (*Continued*).

Observation	*Number of cases in which observation was reported*	*Total*
ANAESTHETIC:		
N_2O (O_2 not stated)	10	
N_2O without O_2	9	
N_2O with O_2	75	99
N_2O, O_2, trichloroethylene	3	
N_2O, O_2, ethyl chloride	2	
COLOUR OF FACE DURING ANAESTHESIA:		
Not cyanosed; not pale	9	
Cyanosed	15	73
Pale	21	
Cyanosed, then pale	28	
PULSE:		
Slow and weak	7	10
Absent	3	
RESPIRATION:		
Stopped	20	
Became feeble	9	75
No change noticed	46	
ARTIFICIAL RESPIRATION:		
Given	24	68
Not given	44	
OXYGEN:		
Given	34	39
Not given	5	
POSITION OF PATIENT AFTER ANAESTHESIA:		
Left upright	4	
Tilted back in chair	20	54
Placed on floor	15	
Placed on couch	15	
CONVULSIONS DURING OR AFTER ANAESTHESIA:		
Seen	3	60
Not seen	57	

TABLE III

ANALYSIS OF 99 CASES OF DELAYED RECOVERY

Observation	*Number of cases in which observation was reported*	*Total*
PLACE OF OCCURRENCE:		
Dentist's surgery	75	
Hospital or clinic	9	92
Dental teaching hospital	8	
AGE OF PATIENT (Years):		
Under 15	26	
15–20	10	96
21–40	37	
Over 40	23	
SEX OF PATIENT:		
Male	27	
Female	59	86
NUMBER OF TEETH EXTRACTED:		
1–3	33	
4–6	17	70
More than 6	20	
PRE-ANAESTHETIC MEDICATION:		
Given	6	74
Not given	68	
ANAESTHETIST:		
Dentist making extractions	17	
Another dentist	13	79
General medical practitioner	39	
Specialist anaesthetist	10	
ANAESTHESIA MACHINE:		
'Walton'	27	
'McKesson'	13	47
'Jectaflow'	3	
Other	4	

TABLE III (*Continued*)

Observation	*Number of cases in which observation was reported*	*Total*
ANAESTHETIC:		
N_2O (O_2 not stated)	10	
N_2O without O_2	9	
N_2O with O_2	75	99
N_2O, O_2, trichloroethylene	3	
N_2O, O_2, ethyl chloride	2	
COLOUR OF FACE DURING ANAESTHESIA:		
Not cyanosed; not pale	9	
Cyanosed	15	73
Pale	21	
Cyanosed, then pale	28	
PULSE:		
Slow and weak	7	10
Absent	3	
RESPIRATION:		
Stopped	20	
Became feeble	9	75
No change noticed	46	
ARTIFICIAL RESPIRATION:		
Given	24	68
Not given	44	
OXYGEN:		
Given	34	39
Not given	5	
POSITION OF PATIENT AFTER ANAESTHESIA:		
Left upright	4	
Tilted back in chair	20	54
Placed on floor	15	
Placed on couch	15	
CONVULSIONS DURING OR AFTER ANAESTHESIA:		
Seen	3	60
Not seen	57	

TABLE III (*Continued*).

Observation	*Number of cases in which observation was reported*	*Total*
BEHAVIOUR DURING UNCONSCIOUSNESS.		
Limp and motionless	32	
Purposeless movements	5	43
Violent	6	
ESTIMATED DURATION OF UNCONSCIOUSNESS:		
Less than ¼ hour	15	
¼–½ hour	13	72
½–1 hour	27	
More than 1 hour	17	
ESTIMATED DURATION OF STUPOR FOLLOWING UNCONSCIOUSNESS:		
¼–½ hour	7	
½–1 hour	20	56
1–2 hours	14	
More than 2 hours	15	
ESTIMATED DURATION OF UNCONSCIOUSNESS + STUPOR (Not differentiated).		
½–1 hour	8	23
More than 1 hour	15	
RECOVERY OF NORMAL HEALTH:		
Unknown	18	
In time not stated	17	
By next day	15	65
By 2 days	3	
By 3 days	5	
By more than 3 days	7	
DISPOSAL:		
Home by taxi or car	43	
Home by ambulance	5	52
Hospital by ambulance	4	

many cases respiration stopped or became feeble; sometimes artificial respiration and oxygen were given, though more often oxygen alone was given. Only three patients had convulsions. Unconsciousness and stupor lasted, as a rule, from half an hour to many hours, but occasionally for days.

During the coma, patients were usually limp and motionless; but six patients were violent. A girl, aged 17, for example, who was "completely unconscious and glassy-eyed, was rough and uncontrollable"; and another girl of 17 became very violent and her legs were bruised and cut.

Some patients were still stuporous when they were sent away; for example, speaking of a man of 50, a dentist said: "We had to half carry him downstairs to get him into a taxi and send him home." Several dentists who sent patients away in stupor never saw or heard of them again.

Forty-six dentists expressed their opinions on the cause of the condition: Neurosis (12), anoxia (7), heart-failure (6), physical weakness (5), shock (3), alcoholism and resistance (3), resistance (2), overdose (2), epilepsy (2), premedication (aspirin, 'Veganin') (2), respiratory failure (1), idiosyncrasy (1).

While the inquiry reported in this Chapter was in progress, I obtained information from other sources.

Chapter IV

SEQUELS OF NITROUS OXIDE IN DENTISTRY: INFORMATION FROM OTHER SOURCES

WITHIN a period of two and a half years beginning in October, 1954, fourteen deaths associated with general anaesthesia for dental extraction in England, Scotland and Wales came to my notice through reports in provincial newspapers. I was able to get information on eight of them. These (Cases 8–15), together with a ninth fatal case (Case 16), which came to my notice by chance, are reported here. Two non-fatal cases (Cases 17 and 18) with severe neurological sequels of uncertain aetiology are reported in Appendix B and Appendix C. All the patients were anaesthetised in the sitting position with nitrous oxide, usually with oxygen. In Case 10, trichloroethylene was added for a few breaths

IMMEDIATE DEATH

Case 8.—A boy, aged 2, convalescent from a respiratory infection, was anaesthetised by a consultant anaesthetist with long experience at a dental teaching hospital. After two incisor teeth had been quickly extracted, the child became pale, stopped breathing, and died ninety seconds after starting to breathe the gas. At necropsy no lesion was found.

Case 9.—A healthy man, aged 22, was anaesthetised with nitrous oxide without oxygen for the extraction of fourteen teeth. He did not seem frightened and was easily anaesthetised. After the teeth had been extracted, oxygen was given because he was cyanosed, but at that moment he became deathly pale and stopped breathing; the pupils dilated and the pulse could not be felt. The anaesthetist attempted to massage the heart externally, while the dentist continued the administration of oxygen, meanwhile, the chair was tilted backwards, after which the patient took a few breaths, but the heartbeat did not return At necropsy nothing significant was found.

Case 10.—A fat but healthy woman, aged 52, was anaesthetised by a specialist for the extraction of ten teeth. She did not seem nervous and took the anaesthetic well. When two teeth had been extracted, respiration suddenly ceased and she became cyanosed. The chair was

tilted backwards and a tube was passed without difficulty into the trachea. The lungs were inflated with oxygen, but the patient was dead. It was estimated that she died within three minutes of starting to breathe nitrous oxide. At necropsy no lesion was found.

Case 11.—A healthy woman, aged 32, was given gas for the extraction of fifteen teeth. Throughout the administration, which lasted no longer than five or six minutes, it was particularly noted that her colour and breathing were normal. When it was stopped oxygen was given. At this moment she suddenly turned pale and stopped breathing. Artificial respiration was at once given and she was placed prone on the floor, but no sign of life returned. At necropsy bloodstained mucus was found at the bifurcation of the trachea, and the lower lobes of the lungs were collapsed. No other abnormality was found.

Case 12.—A healthy miner, aged 46, was given gas for the extraction of 25 teeth after coming off night-shift. The gas was given by the dentist making the extractions, in the presence of his receptionist, who reported that the patient was very easily anaesthetised. After the extractions had been completed oxygen was given for a few moments and he was left to recover. He opened his eyes and looked at the receptionist; his eyes then rolled upwards and closed, his face became grey, and his breathing became very shallow. Smelling salts were given, and then oxygen. After another stimulant had been tried without success, the heart was massaged externally, the chair was tilted backwards and artificial respiration was given, breathing by now having stopped. The measures taken failed to restore either heart-beat or respiration. The main necropsy finding was severe oedema of the lungs, with copious, blood-tinged, frothy fluid in the bronchi and trachea. No pre-existing lesion was found.

Case 13.—A boy, aged 7 years, was given gas at a school dental clinic. The administration was brief and uneventful, and three teeth were quickly extracted. As the patient was recovering from the anaesthetic he cried out. He was taken from the chair to a recovery room where he was found to be collapsed. Jerky movements in his arms made it impossible to inject nikethamide intravenously. He died almost immediately. At necropsy no lesion was found.

Delayed Death

Case 14.—A pale, 17-year-old girl was rapidly and easily anaesthetised. When two or three teeth had been extracted she suddenly became grey, the pupils dilated, and breathing ceased. Her pulse was weak and slow. Artificial respiration and oxygen were given while the dentist continued the extractions, hoping that the stimulus might

revive her. Later, the chair was tilted backwards. Artificial respiration with oxygen was continued while she was transferred by ambulance to hospital, but she died before reaching it.

Case 15.—A policeman, aged 23, was given gas for the extraction of three teeth and the roots of a fourth. He was a tall healthy athletic man, and was anaesthetised without difficulty. The three teeth were quickly extracted, but the dentist then noticed that the patient's breathing had become very irregular. There was no change in the colour of his face, but the dentist stopped the operation at once, gave oxygen and artificial respiration, and tilted the chair backwards. The patient remained unconscious. About an hour later consciousness seemed to be returning, and it was thought that he could shortly be sent home by taxi or bus. A doctor, who had been called, agreed that there was no cause for alarm, but a little later noticed convulsive movements and sent the patient to hospital.

When he arrived, his behaviour was bizarre and he was thought at first to be in a state of hysteria; but very soon his condition was recognised as a sequel to cerebral anoxia. He was having generalised convulsions every two or three minutes, breathing was stertorous, all reflexes (including the corneal) were absent, and there was no response to painful stimuli. He was incontinent of urine. Next morning there was generalised flaccid paralysis and deep coma; all reflexes were absent. His temperature was 104° F. The cerebrospinal fluid was normal. In the evening he died, thirty-four hours after the gas had been given.

A careful necropsy showed no evidence of pre-existing disease. Through the kindness of the pathologist (Dr. A. A. Miller), I was able to arrange for the brain to be sent to the Maudsley Hospital, London, for examination by Professor Alfred Meyer, to whom I am indebted for the photomicrographs (Figs. 4 and 5) and the following histological report:

"*Ammon's Horn.*—There is recent necrosis of part of h_1 and h_2.

unstainable. One large cell shows typical ischaemic degeneration. The remaining small cells show extensive neuronophagia.

"*Cerebellum.*—There is necrosis of some cerebellar lobules. The Purkinje cells have already perished; some show homogenising degeneration. There is proliferation of Bergmann glia and microglial shrubbery of molecular zone.

"This combination of lesions is characteristic of severe cerebral anoxia."

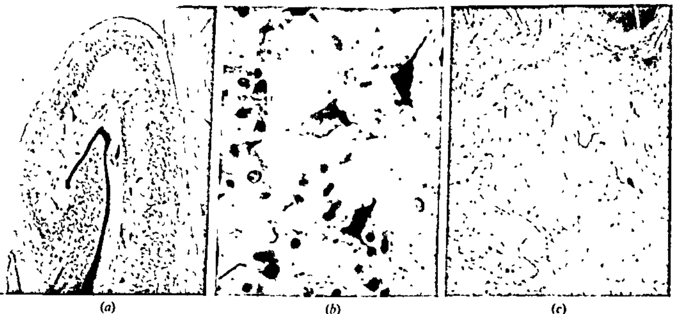


FIG. 4.—*Case* 15. (*a*) Ammon's horn, showing necrosis and loss of nerve-cells in h_1 (Nissl. × 9); (*b*) Ammon's horn showing incrustation and typical ischaemic degeneration of nerve-cells. (Nissl. × 650); (*c*) Putamen, showing patchy staining. (Nissl. × 4·7). (Bourne, 1957*b*).

Case 16.—A thin healthy woman of 44 was given gas for the extraction of two teeth. The administration was brief and simple; the patient was said to have maintained a good colour until it was stopped, when she looked as if she was going to vomit and almost immediately started to have convulsions. She had no history of epilepsy. She was admitted to hospital, where she was found to be in a state of decerebrate rigidity, in which she remained until her death eight days later. At necropsy no macroscopic evidence of

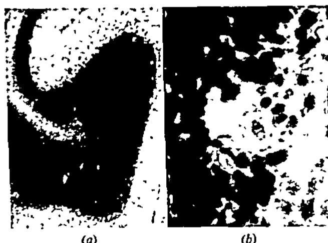


FIG. 5.—*Case* 15 (*a*) Cerebellum, showing loss of Purkinje cells (Nissl × 33); (*b*) Cerebellum, showing homogenising change in Purkinje cell (Nissl. × 630). (Bourne, 1957*b*).

disease was found. The pathologist reported that microscopical examination showed cellular degeneration in the lenticular nuclei, resembling that seen in carbon-monoxide poisoning. He thought it was due to idiosyncrasy to nitrous oxide.

Reviewing the evidence I had collected, the main features of which have been given in this and the preceding Chapter, I felt that the most likely explanation of the sequels in most cases was severe cerebral hypoxia, resulting from patients being kept upright during syncope, and possibly exacerbated by restriction of oxygen in the anaesthetic mixture. In many cases the syncope appeared to have taken the form of a common fainting attack. To test this hypothesis I arranged a study of the circulation of patients under dental gas.

Chapter V

THE CIRCULATION UNDER NITROUS OXIDE IN DENTISTRY: LABORATORY INVESTIGATION

No study of the circulation under dental gas seems to have been made since that of Wright and Thompson (1930). They found that some subjects had a precipitous fall in blood-pressure, which they thought was cardiac in origin. They did not discuss its potential danger in relation to the position of the patient. Methods then available for continuously recording blood-pressure were qualitative only, and not very reliable.

Observations

The recent development of a quantitative and reliable method has made it possible to study afresh the circulatory changes under dental gas Through the kindness of Professor E. P. Sharpey-Schafer, I was able to arrange for a study using this method in the department of medicine at St Thomas's Hospital, to test my fainting hypothesis. I am indebted to him for making the blood-pressure recordings.

Fifteen subjects have been studied, one of whom fainted during anaesthesia They were men who came to hospital as out-patients for extraction of teeth under gas. They were anaesthetised sitting up.

Arterial blood-pressure was measured with a capacitance manometer (Hansen, 1949). The pressure was transmitted to the recording apparatus from a fine needle placed, under local anaesthesia, in the brachial artery at the elbow, which was held at heart level.

The patient who fainted, a man of 31, was pale, but with a normal amount of haemoglobin; ordinarily, his blood-pressure and pulse-rate were normal After the few minutes needed to prepare for pressure-recording he did not seem nervous, and I started to give the gas. I stopped the administration after forty seconds on being warned by the operator of the recording apparatus that his blood-pressure had fallen to a low level. I gave oxygen, tilted the chair backwards, and did not allow the extractions to be attempted.

Just before the gas was started (first arrow, Fig. 6) the heart-rate was 90 a minute and the blood-pressure 75/35 mm. Hg. During the administration the heart-rate slowed to 60 and the blood-pressure fell to 30/15 (second arrow). About then, gas was stopped and

oxygen was given. About at the third arrow the patient was placed supine. This was followed by an increase in blood-pressure and heart-rate to levels higher than before the administration. The oxygen-saturation of arterial blood in the ear* (measured by oximeter) fell to about 65 per cent at the third arrow.

The patient appeared to take the anaesthetic very satisfactorily; there was no movement and his breathing was normal. Neither cyanosis nor increase in pallor was noticed by me or by other ob-

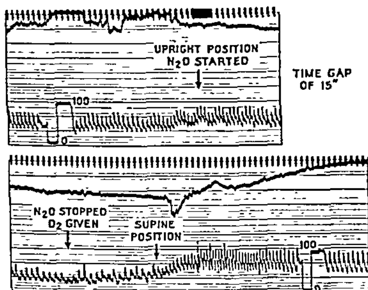


FIG 6—Sections of continuous record of arterial oxygen-saturation (upper tracing) and brachial arterial blood-pressure (lower tracing) in a man, aged 31, during nitrous oxide anaesthesia in the dental chair. There is a time gap of 15 seconds between the sections. Oxygen-saturation at third arrow, about 65 per cent (The [illegible]

servers. When the gas was stopped and the mask lifted, small clonic contractions were seen on the left side of his face; they drew up the corner of his mouth, giving the appearance of smiling.

Full consciousness returned instantaneously when the chair was tilted backwards, and was accompanied by a momentary facial flush. This was followed after a short interval by extreme pallor and profuse sweating, but the patient remained fully conscious, complaining of nausea Half an hour later he felt faint on sitting up and had to lie down again. Malaise and pallor lasted more than an hour. His

* This bears no relation to the oxygen tension in the brain, since the rates of metabolism of skin and brain are very different At that moment the oxygen tension in the brain may have been close to zero.

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be safely anaesthetised, his blood-pressure had fallen to a level at which, in the upright position, cerebral blood-flow probably comes to a standstill (Engel, 1950*a*).

Faints more severe than this have been observed. Eichna and his colleagues (1947) and Greenfield (1951) recorded faints in healthy young men in which there were considerable periods of asystole, the electrocardiogram, in one instance, showing no heart-beat for nineteen seconds. Spontaneous recovery from fainting can take place in the upright position (Anderson *et al.*, 1946), though it is unusual (Engel *et al.*, 1944), and fainting is likely to recur (Engel, 1950*b*). When a patient is kept upright during fainting, therefore, there is always the possibility that his cerebral blood-flow may become arrested and remain in abeyance. When cerebral blood-flow stops, the brain is immediately in danger.

The Brain's Oxygen Reserve.—The metabolism of the brain depends on the oxidation of glucose. Since the brain stores glucose, the effects of sudden arrest of its circulation are those of oxygen lack. At any one moment the brain and the blood within it together contain 7 ml. of oxygen. When its blood-flow stops, the brain, at a normal rate of metabolism,* uses up this quantity of oxygen within ten seconds (Kety, 1950*a*); thenceforward, anoxia is absolute (Gerard, 1938). When the brain is deprived of energy for long enough, functional disturbances, coma, and irreversible cellular damage may result (Fazekas and Bessman, 1953). The question is: how long can the brain be without oxygen and recover completely?

This question may be studied in cases of temporary cardiac arrest; but the time has never been precisely determined in man since it is difficult to define exactly either how long the circulation has been interrupted or what constitutes 'recovery'. Cases have been reported in which the patient was said to have made a complete recovery after days or weeks of disordered cerebral function after a brief period of cardiac arrest (Bailey, 1941; Noble, 1946; Lampson *et al.* 1948; Fox, 1949; Touroff and Adelman, 1949; Lucas, 1950; Turner, 1950; Johnson *et al.*, 1951). But it is difficult to suppose that the brain was undamaged; and there may be degrees of mental impairment that escape notice.

It is generally held that the brain can withstand up to four or five minutes of anoxia before it is irreversibly damaged, but Brock (1956) has said that it is permanently damaged after three minutes.

* The brain's metabolism would not continue at normal rate after abrupt circulatory arrest, it would slow down as oxygen tension fell, and therefore absolute anoxia would not be reached for longer than ten seconds This may account for the fact that, although consciousness is lost in four to five seconds, the respiratory centre does not make its last gasp until twenty to thirty seconds after circulatory arrest.

sensations when the gas was started were identical with those he had experienced previously with gas for dental extraction, when it had had no ill effect; he felt apprehensive, but not faint or sick.

Another patient fainted in the chair after arterial puncture and before anaesthesia was started; he lost consciousness, and there were small clonic twitchings in the face. He regained consciousness at once when placed supine, but became pale. A few minutes later, when raised upright, he fainted again. He was anaesthetised supine and the extractions were made, during which his blood-pressure rose and he became less pale.

Another patient, who fainted before anaesthesia was started and who recovered on being placed supine, was anaesthetised upright without fainting and the extractions were made. He fainted again the moment the anaesthetic was stopped, but instantly recovered on being placed supine. His systolic blood-pressure in the second faint fell to about 40 mm. Hg.

In several other patients low blood-pressures and rapid heart-rates suggested that fainting was imminent, but they were anaesthetised upright without fainting. Their blood-pressures increased during anaesthesia, though the increase was small unless respiration became obstructed.

Comment

Fainting is ordinarily trivial and harmless: the subject falls down or is laid flat, regains consciousness at once and soon recovers completely. During the war more than 25,000 blood donors in the United Kingdom fainted, and all recovered (Barcroft and Edholm, 1945). In dentists' surgeries some patients faint directly their mouths are propped open (*British Journal of Dental Science*, 1889), or even the moment they sit in the chair (*British Journal of Dental Science*, 1897). Most of the faints that dentists see follow the injection of local anaesthetics; it appears to have been overlooked that the patient may also faint while he is being given gas. Fainting is then dangerous because its onset is easily mistaken for the onset of anaesthesia, and the vital step of laying the patient flat may be taken too late.

The Danger of Fainting under Gas.—The danger was clearly seen in the patient who fainted while being given gas during the recording of his blood-pressure, when we failed to recognise the onset of the attack even though we were watching for it. This is not surprising, since the main features of fainting—loss of consciousness and relaxation of muscles—are also the main features of anaesthesia. We mistook them for signs that the administration was progressing satisfactorily; but, at the moment when we believed the patient to

Chapter VI

SEQUELS OF NITROUS OXIDE IN DENTISTRY: DISCUSSION OF CAUSATIVE FACTORS

EPILEPSY and stroke may have sequels closely resembling those of acute cerebral anoxia (Engel, 1950*c*). There are four conditions, therefore, that might, if they accompanied the administration, give rise to disturbance of cerebral function after dental gas: epilepsy, stroke, fainting and anoxia due to excessive restriction of oxygen in the anaesthetic mixture. Hysteria and hyperventilation have also to be considered.

Epilepsy.—I myself observed in Case 18 (Appendix C) an episode of unconsciousness and stupor lasting more than half an hour, after an adminstration of nitrous oxide that had terminated in a typical grand mal attack. The patient was supine, and her lungs were inflated with oxygen the moment the attack began. Her colour remained normal, and her pulse strong; at no time was there either lack of oxygen or hypotension.

The sequels of this attack might easily have been mistaken for those of anoxia, such as might arise from a patient being kept upright in a fainting attack. But epilepsy and fainting may also be difficult to distinguish in the actual attack. For fainting commonly gives rise to convulsive movements (Symonds, 1951), which may, even in patients not subject to epilepsy, develop into a full-blown epileptic seizure. The difficulty in distinguishing between the two conditions would be still greater in a patient under dental gas, which itself gives rise to cyanosis and convulsive movements; and, in the cases reported to me by dentists, little help could be got from the patient's previous history, since this had seldom been enquired into. It might seem, therefore, that cases of delayed recovery could be explained on the basis of epilepsy.

There are, however, reasons for thinking that epilepsy is rare as a cause of delayed recovery after dental gas. In known epileptics, attacks seldom occur with gas. Hewitt (1897*c*), in a wide experience of giving gas to epileptics for dental extraction, never encountered an attack. Furthermore, gross disturbance of cerebral function lasting as long as half an hour after an epileptic attack is unusual except after a generalised convulsion (Stevenson, 1952). In fainting,

Study of case reports (Nystrom, 1930; Schwartz and Jezer, 1932; Lewis, 1939; Rossen *et al.*, 1943; Swan *et al.*, 1952; Zoll *et al.*, 1954), in which the period of cerebral circulatory arrest was fairly accurately known, leads me to think that the time is even shorter than that given by Brock. The reports suggest that, whereas an arrest of nearly two minutes allows immediate recovery of normal function, even a small extension of this time is followed by severe sequels. Two and a half minutes of arrest, for example, may be followed by disturbance of consciousness lasting several hours. An interval, therefore, of about two minutes appears to be critical. This conclusion is in good agreement with experimental findings in animals.

Animal Experiments.—In the dog, cerebral circulatory arrests of two minutes, four minutes, and six minutes may be followed, after periods of coma and stupor, by a return to completely normal behaviour (Kabat and Dennis, 1938 and 1939; Dennis and Kabat, 1939; Kabat *et al.*, 1941; Grenell, 1946; Horiuchi, 1955). It should be noted, however, that dogs after only two minutes of arrest, after which their progress to recovery resembled that seen in some of the non-fatal dental cases, were found to have sustained permanent neuronal damage in the cerebral cortex and cerebellum. Dogs that eventually made a full functional recovery after four minutes and six minutes of arrest, and were able to do tricks they had previously learned, were found to have very severe brain damage (Kabat and Schadewald, 1941; Grenell, 1946; Horiuchi, 1955). In the cat similar results were obtained, though this species withstood slightly longer periods of anoxia before damage could be unequivocally identified (Grant *et al.*, 1939; Weinberger *et al.*, 1940*a* and *b*)

Conclusions

These observations suggest that, to cause delayed recovery of consciousness after dental gas, cerebral hypoxia must be of a severity and duration equivalent to nearly two minutes, at least, of complete absence of oxygen in the brain. Moreover, the animal experiments make it difficult to exclude the possibility that even in the less severe dental cases, which seemed to recover completely quite soon, the brain may have received permanent neuronal damage.

convulsive movements are usually minor and local, and rarely generalised (Weiss, 1935*a*; Engel, 1950*d*); under gas they might easily escape notice, or be regarded as jactitations. In the 60 cases reported to me in which the presence or absence of convulsions was commented on, in only three were convulsions noticed, and in each case they occurred when the condition of the patient had already given cause for alarm. Even these, therefore, are more likely to have been due to fainting than to epilepsy. The striking features in the cases most fully reported were pallor, sweating, limpness, feeble or absent respiration, and dilatation of the pupils, giving the patient a death-like appearance characteristic of fainting not epilepsy. Several dentists thought the patient was dead.

Stroke.—In most of the cases of delayed recovery the patients were children or young adults, in whom stroke is extremely uncommon. In the less severe cases, the course run was not consistent with stroke; and in the more severe cases, the paucity of localising signs and the absence of blood in the cerebrospinal fluid made stroke unlikely. In the fatal cases, stroke was excluded at necropsy. Therefore, stroke is probably rare as a cause of delayed recovery after gas, although isolated examples might occur.

Hysteria.—Several dentists in my survey believed that the manifestations they were reporting were those of neurosis or hysteria; and in Case 15, in which the patient died without regaining normal consciousness, he was at one stage thought to be hysterical. It is a common mistake to regard the sequels of anoxia as hysterical (Steegmann, 1951). They are in fact manifestations of organic dementia. But the dementia may be so profound as to lead to the erroneous diagnosis of hysterical pseudodementia: the patient is so mad that he appears to be aping madness (Meyer, 1956). The characteristics of hysteria (Stevenson, 1952) do not in fact resemble those of delayed recovery after gas. And hysterical fits are out of fashion these days (Richardson, 1952).

Hyperventilation.—Hyperventilation also can be excluded as a cause of delayed recovery, although it often accompanies the administration of gas. Loss of consciousness when it arises from hyperventilation is brief (Stevenson, 1952).

To explain the sequels, therefore, there remains only anoxia, either of stagnant or of anoxaemic origin, or both combined.

Fainting.—It is not surprising that a considerable proportion of the patients whose circulation under gas was investigated, fainted or came near to fainting at one stage or another in the procedure, faced as they were with the formidable surroundings of the laboratory and with hypodermic needles. But fainting is common also in dentists' surgeries, and a final precipitating factor may be fear of the

extracted, after which "she remained unconscious for about a minute with considerable pallor and feebleness of pulse. The author bent her forwards in the chair with her head low. Recovery was gradual, with a feeling of 'pins and needles'." Another patient of Hewitt's (1907*b*), who was anaemic, reached the stage of having convulsive movements after only three breaths of nitrous oxide, an interval too short to be accounted for except by fainting, to which an anaemic patient would be particularly prone. Hewitt believed that epileptiform movements coming on vary early in an administration indicated anaemia. Possibly, however, both the pallor that he noticed in these patients and the convulsive movements were manifestations of fainting. Although Hewitt believed that the sitting posture contributed to the pallor, feebleness of pulse and faintness that he had noticed after gas in some cases, he too thought that in the dangerous and fatal cases some undetected asyphyxial factor had been present (Hewitt, 1907*a*, *c*, and *d*). He appears to have overlooked the possibility of fainting and its consequences.

More recently, Macintosh and Bannister (1952*h*) report having seen about twelve cases of "collapse" early in anaesthesia in children, in whom prompt treatment brought about recovery. The children, they noticed, were immoderately docile and showed no fight; resistance was strikingly absent. Respiration was shallow from the start and unconsciousness came on quickly. Macintosh and Bannister state that if this sudden and unpredictable response to a small amount of anaesthetic is overlooked and more anaesthetic is given, extreme loss of muscular tone and wide dilatation of the pupils may result. They attribute the condition to an undue susceptibility to the anaesthetic: in the light of the present study, the "collapse" seems better explained by fainting. Macintosh and Bannister (1952*i*) give warning of the ease and suddenness with which respiration may become arrested when gas is given to an anaemic patient. Here also, perhaps, both the pallor that suggests anaemia and the respiratory arrest may be due to fainting.

Fainting in the dental chair has been the cause of prolonged unconsciousness when no anaesthetic of any kind had been used (Coleman, 1915); and, in a robust girl of 18, it caused stupor lasting four or five days, followed by a "nervous fever" which continued for months. When last heard of, four years later, this patient was still an invalid (Truman, 1890).

Fainting may also account for some of the fatalities that have occurred with dental gas. Weiss and Wilkins (1937) have pointed out that the heart, as well as the brain, is endangered by the ischaemia of fainting, which may, in subjects kept upright, cause instantaneous death from asystole or ventricular fibrillation (Weiss, 1940). Thus,

(1869) and Kempton (1869), to which I referred in Chapter I, the patients were young girls (aged 11 and 17). The same year Ashford (1869) reported a case in which the patient, again a young girl (aged 16), remained unconscious for two hours after gas. When she started to go home she "grew faint and dizzy, and remembers little that occurred until next morning, when she found her left arm useless." She had hemiplegia and choreiform movements. In this case the feelings of faintness that the patient experienced when she got up to go home suggest that she may have fainted under the gas—once fainting has occurred, the tendency to faint again may persist for hours (Engel, 1950*e*). And the fact that the brain lesions were unilateral does not exclude fainting; nor is it conclusive evidence of stroke. For focal and unilateral lesions can result from low blood-pressure states, without any acute lesion of cerebral blood vessels (Bean and Read, 1942; Cole and Sugarman, 1952; Corday *et al.*, 1953). Again, in two cases described by Clement (1928) the features are suggestive of fainting. A boy aged 4, who was noticeably pale and nervous, remained unconscious after the anaesthetic and had convulsions followed by stupor, with recovery next day. Another boy, aged 7, became an "ashy grey color" during the administration. His breathing stopped and his pupils dilated. Five to ten minutes later, he began to have convulsions. After a period of coma and stupor he recovered. Clement attributed these accidents to excessive restriction of oxygen due to the inexperience of the anaesthetist. The same explanation was given by Seldin (1947*d*) in four cases that he reported; but here also the main cause may have been fainting. In one case, that of a young woman, the features are particularly suggestive of fainting After only a few breaths of nitrous oxide, her respiration became feeble and the pupils dilated. She was given oxygen but remained unconscious and the teeth were extracted. She was "completely relaxed and flabby, and the skin became clammy and cold." Later, she was dazed, unable to co-ordinate, mumbled incoherently and behaved in a demented fashion. After four or five hours, she recovered.

There are records, also, of other instances in which the features [illegible]

the patient nearly losing his life through administration of the gas." The administration was brief, but the patient's breathing stopped and he appeared "quite pallid, as if dead". Hewitt (1907*a*) described the case of a very tall girl, aged 20, who was in the habit of fainting in hot rooms and in church. She took the gas well and one tooth was

fluid was normal. These features are characteristic of the survival period in a patient who has suffered an acute and lethal episode of cerebral anoxia that is not immediately fatal.

In most of the fatal cases that I have reported in Chapter IV, fainting may have been the main cause of death, though in some restriction of oxygen in the anaesthetic mixture may have played an important part.

Restriction of Oxygen.—When a patient faints while being given gas, no doubt the usual cause is fear. But fainting may also be caused by breathing mixtures low in oxygen. This was discovered by Schneider (1918) in airmen undergoing altitude tests, and was actually made use of by Anderson *et al.* (1946), using 7–10 per cent oxygen in nitrogen, to induce fainting in volunteers for experimental purposes. It may account for faints that are delayed until the administration of gas is stopped. Restriction of oxygen, however, may give rise to other dangers.

The practice of compensating for the low potency of nitrous oxide by restricting the supply of oxygen was shown by Courville (1936 and 1939) to result, on occasion, in fatal or crippling brain damage, even in patients anaesthetised supine, in which position fainting is exceedingly unlikely. Courville's findings are substantiated by the overwhelming evidence of numerous case reports by other authors (Olow, 1912; Salzer, 1912; Atkeisson, 1923; Caine, 1923; Yaskin, 1931; Lowenberg *et al.*, 1936; Ford *et al.*, 1937; Brown *et al.*, 1938; Lowenberg and Zbinden, 1938; Stewart, 1938; Steegmann, 1939; Turino and Merwarth, 1941; Kasin and Parker, 1942; Suggs, 1943; Haguenau and Christophe, 1950). As a result of Courville's studies, the practice of restricting oxygen during the administration of nitrous oxide has been abandoned except for minor operations, which, it is thought, do not require restriction of the severity and duration needed to produce harmful effects. And in support of this contention is the fact that restriction of very great severity was used repeatedly in the same individual in certain parachuting experiments (Pask *et al.*, 1943) and in experiments with anoxia in the treatment of schizophrenics (Himwich *et al.*, 1938; Alexander and Himwich, 1939; Fraser and Reitmann, 1939; Fogel and Gray, 1940; Levine and Schilder, 1940; Himwich and Fazekas, 1942), without any marked sequels or delay in recovery of consciousness. The subjects of these experiments were, of course, under very close supervision; but in anaesthesia, it is supposed, the signs of severe oxygen lack are too alarming to be neglected, and the cerebral hypoxia could be quickly reversed by giving air or oxygen (Macintosh and Bannister, 1952*a*).

It is probable, however, that cerebral hypoxia of respiratory origin is harmless in degree and is readily reversible only so long as

according to Weiss, fainting is sometimes the cause of death in elderly patients who die suddenly on getting out of bed after prolonged rest, the danger is particularly great if they are propped up in a chair so that the body cannot assume a horizontal position, when dangerous cerebral ischaemia rapidly results (Weiss, 1935*b*). The Roman crucifixion is an example of death from fainting while the upright position is forcibly maintained (Weiss, 1935*c*), which may also be one of the causes of death in wedged crowds (Sharpey-Schafer, 1956).

In some of the few fatalities with dental gas that have been reported, there are features suggesting that an unrecognised fainting attack may have been the main cause of death. For example, in a case reported by Davies (1931), a youth of 19 died after an administration of dental gas lasting only twenty seconds. He had arrived at the dental surgery without his parent's written consent for anaesthesia. He was therefore sent home on his bicycle, a distance of a mile and a half, to get the consent, and returned, giving a lift to a boy on the carrier. He went under the gas quickly, without becoming deeply cyanosed. The administration was stopped and the mask was removed; but before the extraction could be made, respiration ceased. He was put on the floor and given oxygen and artificial respiration, but he was dead. He was a poorly developed youth who had never been robust, but the exertion of the bicycle ride showed that he had considerable cardiac reserves, and at necropsy the only abnormality found was enlargement of lymphoid tissue. Death was attributed to status lymphaticus, but it seems to me that a more satisfactory explanation is fainting: even healthy athletes kept erect after exercise may faint (Eichna, *et al.*, 1947). It is an attractive hypothesis that the condition formerly known as 'status lymphaticus' may be simply proneness to severe fainting attacks.

Other dental cases in which death under gas occurred suddenly and unexpectedly, and in which it now seems that an unrecognised fainting attack may have been the main factor, have been reported by Mason (1873), *The Lancet* (1877, 1894), Williams (1883), Adams (1894), Buxton (1897), Graham (1904), Owen (1904) and Trumper (1948). And in a case described by Glynn (1926), death may have been due to the same cause, although the patient, a healthy youth, aged 17, did not succumb for thirty-seven hours The administration of the anaesthetic and the extraction together had taken only about a minute. The patient was beginning to recover from the anaesthetic, when "he went a nasty colour . . . and collapsed." From then until death the course of his illness closely resembled that seen in Case 15 (Chapter IV). There was pyrexia, convulsions, incontinence, dementia, and finally coma and terminal pneumonia. The cerebrospinal

Chapter VII

THE POTENCY OF NITROUS OXIDE

THE potency of an inhalational anaesthetic may be expressed in terms of the effect obtained with the anaesthetic at a given concentration. A full effect is not obtained at once; induction may take a considerable time. Moreover, patients differ in their response. A factor that may influence response is the taking of alcohol or other drugs. Therefore, in making a study in man of the potency of nitrous oxide, two factors to be taken into account were the length of time needed to obtain a maximum effect with the anaesthetic at the concentration studied, and the possible influence of acquired tolerance to central nervous system depressants in the subjects used. No such study of nitrous oxide, or indeed of any anaesthetic, appears to have been made.

Time Needed for Maximum Effect.—The length of time needed to obtain a maximum, or near-maximum, effect varies widely with the different anaesthetics for reasons that will be discussed in Chapter VIII. With nitrous oxide the time is relatively short, though less short than is generally supposed by dental anaesthetists, who expect anaesthesia within a minute in patients who take the anaesthetic well. In dental anaesthesia much of the early effect is due, as already noted, to hypoxia. Without hypoxia, induction with nitrous oxide takes several minutes. Mushin (1952) estimates seven to ten minutes; and Kaye (1951) believes that ten to fifteen minutes are needed for a full effect. These estimates, based on clinical experience, are in good agreement with actual measurements made by Kety.

With an inhalational anaesthetic, depth of anaesthesia is governed by the partial pressure or tension of the anaesthetic in the brain; and the rate of induction, or of recovery, is governed by the rate of change of this brain tension (Kety, 1950*b* and 1951). These conclusions are based on experimental evidence obtained by Haggard (1924*d*), using ether in dogs. Haggard (1924*c*) also showed that a direct measure of the ether content of the brain was given by the ether content of blood drawn from the internal jugular vein—a method of measuring brain tensions that is now generally accepted as accurate, within narrow limits, for any dissolved gas or vapour, even when its tension is changing rapidly. Thus the rate of induction with nitrous oxide may be determined by making serial measure-

the circulation remains in a hyperdynamic state, which, in some subjects breathing low-oxygen mixtures (especially when kept upright) soon gives place to a fall in blood-pressure that may be precipitous (Gellhorn, 1937; Gellhorn and Lambert, 1939). In some cases this fall may be due to fainting, but, in the absence of fainting, there may be syncope of another kind—"the syncope of asphyxia, the condition which obtains when cyanosis gives place to pallor" (Hewitt, 1907*e*). Its effect on the cerebral circulation may be no less serious than that of fainting, and may have accounted for Case 7 and other cases reported to me by the dentists in my survey.

This form of syncope was probably the condition produced by McKesson (1920) in his misnamed "saturation" techniques for abdominal and other operations, as is apparent from Boyle's (1934) description:

"When I saw him do this it was an alarming sight. It consisted of giving gas until the pupils were widely dilated, the colour was grey, and the patient looked like death. Then the lungs were distended with oxygen, and gradually the colour returned to pink. 'That is primary saturation,' said McKesson, and then he proceeded to do it all over again."

I have seen "primary saturation" practised today in dental-extraction clinics in London, sometimes accidentally and sometimes deliberately to overcome "resistance." This may have been the cause of the syncope and respiratory arrest in the two cases that I reported in Chapter II.

The harmful effects of restricting oxygen in dental anaesthesia may be summarised as follows: (1) it may cause fainting; (2) it may give rise to syncope of another kind; and (3) it may, in either form of syncope, exacerbate the hypoxia of both brain and heart.

CONCLUSIONS

In nearly every case, delayed recovery of consciousness after dental gas should be regarded as a sequel of severe cerebral anoxia. Probably the main cause of the anoxia is fainting, which could be avoided by giving the anaesthetic with the patient lying down. But an important contributory factor is restriction of oxygen in the anaesthetic mixture, which is potentially dangerous even in the recumbent patient. The practice of administering nitrous oxide with restricted amounts of oxygen should be abandoned in work with ambulatory patients, as it has been in all other fields of anaesthesia.

The next step in this study, therefore, was to make a clinical assay of the potency of nitrous oxide to test the possibility of modifying the method by using nitrous oxide without restriction of oxygen.

yet reached 80 per cent of inspired tension; but thenceforward the increase is slow, full equilibrium being reached only when the entire body has become completely saturated, a process taking several hours. Only then would the maximum effect be obtained. But in actual work with ambulatory patients, to prolong induction even as long as ten minutes would be impracticable. In the present study, ten minutes was the minimum time allowed.

Tolerance to Central Nervous System Depressants.—Tolerance, more correctly cross-tolerance, is a phenomenon known to every dental anaesthetist: patients addicted to alcohol are difficult to anaesthetise with nitrous oxide. They are referred to as 'resistant'. 'Resistance', however, is not confined to inveterate drunkards but extends to a great many people whose daily consumption of alcohol would not be considered excessive (Robinson, 1922*a*). Moreover, since in animals tolerance to alcohol confers cross-tolerance to barbiturates (Goodman and Gilman, 1955*a*), it seems reasonable to expect that 'resistance' might be acquired through habitual use of these compounds, and perhaps also sedatives or hypnotics of other kinds, which nowadays are widely prescribed. In this study, therefore, each subject was closely questioned before anaesthesia on his consumption of alcohol or other central nervous system depressants.

An attempt was made to group the subjects according to the amount of depressants they were in the habit of taking. Very few, however, could give this information even approximately. Often the amount was too variable for classification; and many of those who took sedatives or sleeping draughts were unable to name the drug or dose. In the event, therefore, the patients could be divided into only two groups: those who took no depressants; and those who took them in various amounts.

Other Factors.—Temperament, physique, age, sex and metabolic rate are also believed by dental anaesthetists to have a considerable effect on the patient's response to nitrous oxide. Aggressive, muscular, athletic young men, and patients with a raised metabolic rate, are said to be 'resistant', whereas anaemic, frail or elderly patients, particularly women, are held to be susceptible to nitrous oxide. Note was therefore taken, also, of these factors so that their influence could be studied.

Material

The subjects used were 200 patients admitted to hospital for a variety of surgical procedures ranging from trivial ones, such as endoscopic examinations, to major operations like abdomino-perineal resection of rectum. In 63 of them the operation was

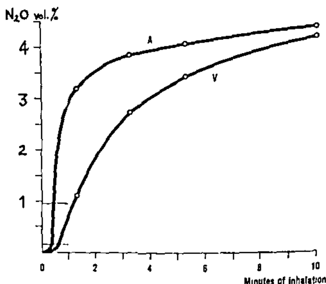


FIG 7.—Typical curves of nitrous oxide tensions in arterial blood (A) and internal jugular blood (or brain) (V) during a ten-minute period of inhalation of 15 per cent nitrous oxide (Kety, 1957)

ments of the anaesthetic's tension in internal jugular blood. Many series of such measurements, with simultaneous measurements of arterial nitrous oxide tensions, have been made by Kety in connection with his nitrous oxide method of measuring cerebral blood flow. Typical curves are shown in Fig. 7.

This figure shows the rate at which the tension of nitrous oxide increases in arterial blood (A) and internal jugular blood (or brain) (V) when the gas is abruptly introduced into inspired air at a constant partial pressure of 15 per cent of an atmosphere. Kety has expressed the view in a personal communication that the shape and time relations of the curves would be the same with any given partial pressure of nitrous oxide short of those resulting in hypoxia, a condition that materially affects the physiological processes governing the uptake of inert gases by the body. On this assumption, which is in agreement with earlier statements by Henderson and Haggard (1927), the venous curve in Fig 7 may be taken as illustrating the rate of increase of brain tension with nitrous oxide at concentrations around 80 per cent—those used in surgical practice (other than out-patient work) and in the present study. The rate of recovery on withdrawing the anaesthetic would be represented by the same curve inverted (Kety, 1951).

It will be seen that even after ten minutes the tension of nitrous oxide in the brain is still increasing. By then brain tension has not

or longer. In many instances a fresh series of observations was made after an hour or more, when the operation had been completed.

The first thing observed was the patient's general behaviour before any stimulus was applied. Next, his response to a simple command, like "show me your tongue", was tested. After this, the eyelid reflex and the response to superficial and deep pain were examined, superficial pain being evoked by applying a sharp upward pull to the hair above the ear, and deep pain by squeezing the Achilles tendon. Some patients were then subjected to operation without any further medication and their reaction to this stimulus was observed. Others were first given a relaxant, which masked their response to the surgical stimulus until the closing stages of the operation, when the effects of the relaxant had passed off or had been neutralised by an antidote. When anaesthesia was clearly inadequate it was supplemented with thiopentone before the operation was begun, bringing the experiment to a close after the initial series of observations had been completed.

Finally, speed of recovery on withdrawing the anaesthetic was timed in some of the patients. Since it was very unlikely that wide differences in speeds of recovery would reflect corresponding differences in rates of elimination of nitrous oxide, it seemed reasonable to assume that speed of recovery would give additional information on the extent to which different individuals were affected by the gas.

Results

Habitual use of depressants was found to have a pronounced effect on the response to nitrous oxide. The two groups of patients are therefore considered separately.

Patients not Habituated to Depressants.—The response of the 66 patients who took no depressants was remarkably uniform. After induction, they lay motionless, with eyes closed, breathing rhythmically, and appeared to be in surgical anaesthesia. They made no response to a simple command. The eyelid reflex was weak or absent. The superficial pain test evoked no response in 45 of them, the remainder responding by a scarcely perceptible movement of the eyelids on the side stimulated or of the head away from the stimulus. The deep pain test evoked no response in 42, and only a feeble contraction of the quadriceps femoris in the remainder.

Forty-seven of the patients were subjected to operation without additional medication, the remaining nineteen being first given a relaxant. In response to the stimulus of the operation, nearly all the 47 moved, but in no case was the movement purposeful. It was limited as a rule to the hands and feet, but sometimes the whole of

extraction of teeth. Most of the patients were adults, but seven were in their first, and nineteen in their second decade. The youngest was five months old, and six were over 80 years old. The sexes were about equally represented.

Sixty-six patients took no depressants, and 134 took them in different amounts. Both groups contained patients exhibiting the various other factors believed to influence the response to nitrous oxide.

Method

The patients were anaesthetised supine. The anaesthetic was given through a cuffed endotracheal tube introduced under brief preliminary anaesthesia with cyclopropane. The procedure was as follows: about an hour before anaesthesia, the patient was given a subcutaneous injection of atropine gr. 1/75 (0·8 mg.) or of scopolamine gr. 1/150 (0·4 mg.) to lessen pharyngeal secretions. (Children in their first decade were given half these amounts; and in their case the tube used was not cuffed). Anaesthesia was induced by allowing the patient to breathe in and out of a six litre bag filled with cyclopropane and oxygen in equal parts. After six to eight breaths, when consciousness was lost, the administration of cyclopropane was stopped and suxamethonium was injected intravenously to provide momentary relaxation for the introduction of the tube. The cuff was then inflated, making an air-tight seal in the trachea, and the administration of nitrous oxide and oxygen was begun. Time was counted from this moment.

The nitrous oxide-oxygen mixture was given from a standard Boyle's apparatus with rotameter flowmeters, the accuracy of which was checked and confirmed with a Parkinson and Cowan gasmeter. About half the patients were given 80 per cent nitrous oxide (flowrates: nitrous oxide, 8 L/Min.; oxygen, 2 L/Min.), and the remainder 83 per cent nitrous oxide (flowrates: nitrous oxide, 10 L/Min.; oxygen, 2 L/Min.). In eight patients the concentration after twelve to fifteen minutes was increased for five minutes from 83 to 91 per cent *(flowrates: nitrous oxide, 10 L/Min.; oxygen, 1 L/Min.)*.

With this method of induction, as the lung and tissue tension of nitrous oxide increases, the cyclopropane is eliminated. My experience with cyclopropane used in this way in ambulatory patients (Chapter X) has shown that all trace of its anaesthetic action disappears after such an administration well within ten minutes. In this study, therefore, the effects observed after this initial phase were solely those of nitrous oxide.

Observations were made after the administration had been in progress not less than ten minutes and in most cases twenty minutes

after the full induction period, were clearly not so at an earlier stage. Anaesthesia was at its lightest at five or six minutes, when the effects of cyclopropane and suxamethonium had disappeared and those of nitrous oxide were still increasing fairly rapidly. At this stage, patients often were moving and were not relaxed; they sometimes had their eyes open; and they responded briskly to a painful stimulus. They did not appear to be in surgical anaesthesia, and probably few would have remained still under the stimulus of surgery unless it was slight. A child aged five, for example, who was to have his tonsils removed, reacted briskly when an attempt was made to perform the operation at five minutes, but at thirteen minutes was satisfactorily anaesthetised.

All the patients in the group considered themselves to have been fully unconscious throughout. They usually said that they lost consciousness after three or four breaths (of cyclopropane) and knew nothing more. Some were surprised to find on regaining consciousness that they had already had their operation.

The rate of recovery from anaesthesia was studied in seventeen patients in the group. All of them, including five who had been under the anaesthetic for more than a hour, regained consciousness in about four minutes, and either by then or within the next minute or so were correctly orientated. For a few minutes longer, however, they remained drowsy.

Patients Habituated to Depressants.—In this group were twelve men who drank never less and usually more than two pints (one litre) of beer a day. Others in the group may have been accustomed to taking larger amounts, but since the consumption of these twelve men was fairly accurately known, they formed a useful sub-group for comparison with the 66 patients who took no depressants. A typical example of their response to nitrous oxide is shown in Fig. 8.

The patient shown in Fig. 8, a drayman aged 48, acknowledged drinking at least five pints of beer a day. The photographs, taken from film (Bourne, 1954*a*), show his behaviour after the administration of 83 per cent nitrous oxide had been in progress more than fifteen minutes. It will be seen that he did not appear even to have lost consciousness His eyes were open, his expression was alert and he 'talked' continuously, though, owing to the presence of the tube, he was unable to phonate. His movements were brisk and purposeful, and scarcely at all ataxic. At one stage he made an accurate attempt to unknot the tape tied round his neck to secure the endotracheal tube. He made no attempt, however, to remove the tube, which he evidently mistook for a pipe of tobacco, since he went through all the movements of striking a match and lighting up.

Figure 9 (Bourne, 1954*a*) shows another of these patients after

one or more extremity made a sudden, brisk and extensive movement, making it difficult or impossible to continue the operation without further medication.

The extent of movement seemed to depend not on differences in depth of anaesthesia between one patient and another but on variations in the intensity of the stimulus or in the sensitivity of the site of operation. An attempt, for example, to remove the great toe-nail in two youths resulted in both cases in sharp withdrawal of the limb. In a five-months old infant undergoing mastoidectomy, the skin incision evoked brisk flexion of the lower extremities and abduction of the upper ones, whereas during the remainder of the operation, which lasted forty-five minutes, there were only minor movements of the hands and feet. Two other children, aged fifteen months and two and a half years, undergoing the same operation reacted in a similar way. Again, two girls aged twelve and thirteen, and a woman aged thirty-three, each of whom was having several teeth extracted, remained still during the easier extractions but moved to an extent that made anaesthesia unsatisfactory when force was applied to make the more difficult ones. The skin in the region of the breast appeared to be especially sensitive. Of six women undergoing operations on the breast all moved, five of them to an extent that brought the operation to a halt; but two men undergoing thyroidectomy, one of them a policeman aged 24, were satisfactorily anaesthetised.

Anaesthesia was satisfactory for the operative treatment of varicose veins and fissure-in-ano, and for the extraction of teeth, respectively, in three healthy, muscular young men, a butcher, a taxi-driver and a lorry-driver, each weighing more than fifteen stone (210 pounds, 95 Kilos)

Of the 47 patients operated on without further medication, anaesthesia was, in fact, satisfactory in 33, though coughing and vomiting, reflexes that are not abolished by this anaesthetic, were troublesome in some of them.

Of the nineteen patients who were given a relaxant before the operation was started, sixteen were having an abdominal operation. Two of these patients, a woman of 66 and a man of 32, flexed their lower extremities briskly in response to suturing the skin at one hundred and fifteen minutes and thirty-nine minutes, respectively, the effects of the relaxant having by then passed off, but the remainder made little or no response to this stimulus. The increase in depth of anaesthesia at the end of a long administration as compared with the depth at the end of the induction period was scarcely perceptible.

Some patients in the group, though satisfactorily anaesthetised



FIG 8 —Response of a drayman to 83 per cent nitrous oxide given for more than fifteen minutes Sequences from film (Bourne, 1954*a*).

the induction phase had been completed. This patient, a man of 57, continually tried to remove the tube, half sitting up in his efforts to get hold of it; considerable force was needed to restrain him.

The upper photograph shows the patient's response to 83 per cent nitrous oxide; the lower one was taken after the concentration had been raised for five minutes to 91 per cent. Apart from making him cyanosed, the only effect of increasing the concentration was to slow down slightly and weaken his movements; but they did not lose their purposeful character or their accuracy. He continued to 'talk' as he had done before the concentration was raised.

Several of these patients obeyed simple commands. For example, a farm labourer, aged 67 and weighing nine stone (126 pounds; 57 Kilos), turned and looked at me at ten minutes when I addressed him by name; and on being told to clasp his hands in front of his chest he at once did so. At seventeen minutes he was 'talking' and beckoning to me, and grasped my hand.

This kind of response was not limited to the twelve men so far referred to. Of the 134 patients who took depressants, 38 reacted to a greater or less extent in this manner. Most striking of all was the response of an emaciated army officer, aged 45, who was within three weeks of his death from carcinomatosis arising from a growth in the head of the pancreas. For many months he had received heavy doses, at first of sedatives, when his complaint was believed to be functional, and then of morphine and its analogues. This patient, after breathing 80 per cent nitrous oxide for twelve minutes, was sitting bolt upright, 'shouting' and gesticulating

All 38 patients were given thiopentone to supplement the anaesthetic before the operation was started. None of them had any recollection afterwards of any phase of the procedure. Like the group who took no depressants, they felt that they had lost consciousness after a few breaths of cyclopropane and had remained unconscious until after anaesthesia had been discontinued.

The remaining patients in the group gave intermediate responses, some approaching the extremes I have described, others bordering on a state of true surgical anaesthesia like the patients who took no depressants Many of them, while clearly unconscious, reacted briskly to painful stimuli In response to the superficial pain test, they screwed up their faces as if in pain and moved their heads away; and in response to the deep pain test, they briskly withdrew the extremity. Some who were given only a relaxant for the operation and not a supplementary anaesthetic, showed these pain reactions in response to suturing the skin at the end of the operation, when the effect of the relaxant had passed off. One of these did not fully lose consciousness and experienced pain.

He was a head gardener, an intelligent man of 45, undergoing amputation of penis for carcinoma. He gave his weekly consumption of beer as three to four pints taken on Saturday night. Throughout the operation he reacted briskly as the effects of suxamethonium passed off, necessitating repeated injections of this relaxant. When the operation was completed and he had recovered from the anaesthetic, he was distressed. He said that he had failed to reach the point where consciousness completely disappeared. He had been entirely unaware of his surroundings; he had seen nothing and heard nothing, and he had been unaware of the presence of the endotracheal tube. Nevertheless, he had experienced pain, which came in waves and which he was unable to locate because, as he put it, "I lost all my shape". In this state of delirium he had identified loss of consciousness with death. He was therefore afraid of losing consciousness completely, although he wanted to do so to escape the pain. He was subsequently anaesthetised for another operation with thiopentone and nitrous oxide, which, he said, made him completely unconscious and was entirely satisfactory. Another patient, whose muscles had been paralysed with a relaxant for teeth extraction under the anaesthetic, kept shaking his head on regaining consciousness, as if to clear his mind, and went on repeating "what a shambles". He assured me, however, that he had felt no pain and had been quite unconscious of the operation.

The effect of habituation to depressants was clearly shown by the response of three girls, aged 18, who were having teeth extracted and who were alike in weight and in physical appearance. Two of them took no depressants and were satisfactorily anaesthetised. The third had been in the habit for two years of drinking gin, perhaps daily. (She was an unreliable witness.) This patient did not seem to lose consciousness. Even when the administration of nitrous oxide had been in progress for twenty-five minutes she obeyed simple commands. When asked, "Can you lift your head off the pillow?" she nodded and then did so, holding it up until asked to put it down again. However, she had no recollection afterwards of these events and believed herself to have been unconscious.

Some of the patients in this group regained consciousness almost immediately the anaesthetic was stopped. Speech in those who were 'talking' at this moment was usually rambling and inarticulate at first, but within a minute it became articulate and even rational. A man aged 54, who drank four pints or more of beer a day, spoke coherently from the start, and after a few breaths was correctly orientated; and two women who had been taking barbiturates daily for a year, as well as small amounts of alcohol, and who had reacted briskly under the anaesthetic to the stimulus of extraction of teeth,





Fig 9.—The response of a man, aged 57, who drank considerable amounts of beer: *above*, to 83 per cent nitrous oxide, *below*, to 91 per cent nitrous oxide (Bourne, 1954*a*)

He was a head gardener, an intelligent man of 45, undergoing amputation of penis for carcinoma. He gave his weekly consumption of beer as three to four pints taken on Saturday night. Throughout the operation he reacted briskly as the effects of suxamethonium passed off, necessitating repeated injections of this relaxant. When the operation was completed and he had recovered from the anaesthetic, he was distressed. He said that he had failed to reach the point where consciousness completely disappeared. He had been entirely unaware of his surroundings; he had seen nothing and heard nothing, and he had been unaware of the presence of the endotracheal tube. Nevertheless, he had experienced pain, which came in waves and which he was unable to locate because, as he put it, "I lost all my shape". In this state of delirium he had identified loss of consciousness with death. He was therefore afraid of losing consciousness completely, although he wanted to do so to escape the pain. He was subsequently anaesthetised for another operation with thiopentone and nitrous oxide, which, he said, made him completely unconscious and was entirely satisfactory. Another patient, whose muscles had been paralysed with a relaxant for teeth extraction under the anaesthetic, kept shaking his head on regaining consciousness, as if to clear his mind, and went on repeating "what a shambles". He assured me, however, that he had felt no pain and had been quite unconscious of the operation.

The effect of habituation to depressants was clearly shown by the response of three girls, aged 18, who were having teeth extracted and who were alike in weight and in physical appearance. Two of them took no depressants and were satisfactorily anaesthetised. The third had been in the habit for two years of drinking gin, perhaps daily. (She was an unreliable witness.) This patient did not seem to lose consciousness. Even when the administration of nitrous oxide had been in progress for twenty-five minutes she obeyed simple commands. When asked, "Can you lift your head off the pillow?" she nodded and then did so, holding it up until asked to put it down again However, she had no recollection afterwards of these events and believed herself to have been unconscious.

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became conscious within a minute of stopping the anaesthetic. Two women who were teetotal but took a nightly dose of barbiturate were also insufficiently anaesthetised and regained consciousness after the anaesthetic was withdrawn in much shorter time than was seen in the group of patients who took no depressants.

Dental Cases.—Of the 63 dental patients, 21 were in the group who took no depressants. Anaesthesia was satisfactory in 18 of these. Of the 42 who took depressants, anaesthesia was satisfactory in 21.

Six of the dental patients were men in whom an attempt to establish anaesthesia with nitrous oxide in dentists' surgeries had failed. It was for this reason that they were being treated as in-patients When tested in the present investigation, nitrous oxide gave satisfactory anaesthesia in three of them. These were healthy, muscular young men, who took little or no depressants. Two of them weighed over twelve stone (168 pounds; 76 Kilos). Anaesthesia was unsatisfactory in the other three. Their ages were 21, 38 and 63, and they all drank considerable amounts of beer. The oldest of them drank several pints a day and was one of the patients referred to above who did not seem to lose consciousness under the anaesthetic.

Absence of Shock.—In none of the 200 patients did the lightness of anaesthesia have any adverse physical effect. Pallor and sweating occasionally accompanied retching and vomiting when they occurred, but the pulse rate did not increase, nor did the blood pressure fall. Shock was not seen.

Discussion

Reviewing the pharmacology of nitrous oxide and other anaesthetic gases, Seevers and Waters (1938) found a "lack of accurate quantitative data concerning nearly every phase of nitrous oxide anesthesia". The potency of nitrous oxide, they said, had never been clearly determined. Published reports were on experiments in small animals and there was a need, they thought, for further experimentation in larger animals such as the dog or man

A study in man had, in fact, been reported a year previously by Seevers, *et al.* (1937). Their subjects were ten young men, students and laboratory workers. They found that the concentration of nitrous oxide needed to produce unconsciousness showed great individual variation. Most of the men did not lose consciousness and were able to co-operate during continuous inhalation of 35 to 40 per cent, and two of them could remain on their feet for five minutes while inhaling 60 per cent nitrous oxide The level at which consciousness was lost varied between 35 and 70 per cent.

Similar results emerged from incidental observations made by Frumin (1957) in a study undertaken for other purposes. His

patients were subjected to operation under nitrous oxide and a relaxant; but some of them (it is not clear which) were also given depressants as pre-anaesthetic medication and small doses of thiopentone for induction of anaesthesia. He found that concentrations of nitrous oxide between 50 and 61 per cent did not always abolish consciousness. The patients remembered hearing conversations that had taken place in the operating theatre and a few of them experienced pain. One patient, having an orthopaedic operation, did not lose consciousness with 71 per cent nitrous oxide, but felt no pain. With 65 per cent nitrous oxide, patients almost invariably responded to a simple command. Frumin occasionally got a response to command from patients under 80 per cent, and from one patient under 86 per cent nitrous oxide, though none of these had any recollection post-operatively of what had taken place. Some of them, however, had had vivid and unpleasant dreams related to the operation.

Frumin's observations had not been published at the time of my investigation. That a patient under high concentrations of nitrous oxide could experience pain was therefore totally unexpected. For it has always been universally believed that pain is the first sense to be dulled by anaesthetics, particularly nitrous oxide, and that it disappears long before sight or hearing are lost. And, in fact, 'Stage of Analgesia' is the name given to the stage of induction that precedes loss of these functions. Frumin's patients who felt pain had not apparently lost their sense of hearing; but in my patient, pain was the only sense left. It was in the belief that pain would invariably be abolished that I embarked on this investigation: my experience with this patient led me to question the anaesthetic's supposed analgesic properties and to proceed more cautiously.

Neither Frumin nor Seevers and his colleagues related the wide individual variation in response to nitrous oxide to the influence of acquired tolerance to central nervous system depressants, a possibility that they do not seem to have considered

My investigation suggested that this influence was of paramount importance. Acquired tolerance appeared to be not simply the main, but the only factor influencing a patient's response to nitrous oxide after the induction period. If other factors played a part, their influence was too small to be detected clinically. Thus in patients who took no depressants, the effect of nitrous oxide was predictable. Infants, children, robust young men and frail or elderly patients were all anaesthetised to the same level—a level that closely approximated to true surgical anaesthesia.

This level of anaesthesia was satisfactory for procedures that did not evoke much pain, but considerable reflex movement was liable to occur if sensitive structures were involved. It seemed doubtful,

for example, whether nitrous oxide would ever give satisfactory anaesthesia for the removal of the great toe-nail, a procedure that Liston (1847), whose operative experience was gained in the years that preceded the discovery of anaesthesia, referred to as one of the most painful operations in surgery. For the extraction of teeth, however, I found that nitrous oxide gave satisfactory anaesthesia in all [illegible]

and 1955) for his method of using nitrous oxide. This differed from standard practice in two ways: an atmospheric amount of oxygen was given with the gas from the outset; and the administration was continued for three to five minutes or longer before the operation was allowed to be started, the anaesthetic being given nasally, as in standard practice. Reference to Fig. 7 will show that this length of induction gives time for at least partial saturation of the brain with the gas. Klock's method, therefore, is of special interest; for it was, in fact, a trial in actual dental practice of the very question at issue in the present investigation—whether nitrous oxide was capable of giving satisfactory anaesthesia when oxygen was not restricted. Unfortunately, Klock, working in the United States of America, gave no details of his patients. In the United Kingdom about half those anaesthetised in dental practice are children; and in the remainder, women greatly outnumber men. In children saturation of the brain takes place more rapidly than it does in adults (Henderson and Haggard, 1927); and in women and children tolerance is probably less commonly encountered than it is in men. For these reasons, dental patients given gas in this country may be more suitable subjects for nitrous oxide anaesthesia than were those in the sample I investigated If the same is true in the United States of America, it would not be surprising if Klock met with a greater measure of success with nitrous oxide than I did in the present investigation.

He found that patients responded after the induction period to simple commands, but post-operatively had no recollection of the operation or of having felt pain. He believed they reached a stage in which memory rather than consciousness was abolished and which lay at the threshold of the well-recognised second stage of anaesthesia, the stage of excitement or delirium, as it is called. If anaesthesia became deeper they were liable to become excited, and he found it advisable to have restraining straps placed ready for use. In about 10 per cent of his cases, nitrous oxide was not powerful enough to induce the required level of narcosis and a more potent anaesthetic had to be added.

Tom (1956), in the United Kingdom, confirmed Klock's findings

and reported favourably on the method. Nearly all his patients were children. A difficulty he found was to maintain nasal breathing. A strong stimulus caused the patient to revert to mouth breathing, whereupon anaesthesia quickly became too light. It was then necessary to interrupt the dentist's work and cover the mouth until nasal breathing was re-established. Neither Klock nor Tom* stated in what proportion of cases the method failed, but it would be unlikely to succeed in patients who were 'resistant'.

This term is applied to patients who struggle, and there is general *agreement that the most troublesome in this respect* are heavy drinkers. However, 'resistance' cannot be explained on the basis of tolerance alone since it is seen in dental practice in patients who take no depressants, notably in strong, athletic young men. Its occurrence in such patients may be explained by the fact that, in everyday practice in ambulatory patients, induction with nitrous oxide is seldom if ever continued long enough to get beyond the stage of delirium, which is characterised by loss of conscious control and by a tendency for the patient to become excited and struggle. Strong young men who struggle may become completely uncontrollable, and it may be their uncontrollability rather than their proneness to become excited that has given rise to the impression that they are particularly 'resistant'. Clement found that sometimes a powerful patient succumbed readily to the anaesthetic and a small, frail one proved very 'resistant' (Clement, 1951g). In the series reported in Chapter II, some of the most difficult patients were women and children. It seems, therefore, that behaviour during induction with gas largely depends on how the patient is disposed to behave when conscious control is lost, and this cannot be foreseen.

In patients who take no depressants, struggling would subside if the administration could be continued until induction was completed. But this may require ten minutes, during which struggling might make continuance difficult or impossible. In patients who have become tolerant to depressants, the deeper level is unattainable. It remains to be *considered to what extent tolerance may raise a* patient's threshold to anaesthesia.

In the dog, tolerance to alcohol can be developed to a degree that allows an animal to walk about and climb stairs at blood alcohol levels that leave a control animal in coma (Newman and Card, 1937). Man may become tolerant to a hundred times the normal therapeutic dose of morphine (Fraser, 1957); Kilpatrick (1955) reported the case of a woman who was able to remain at work and drive her car while

* In a personal communication Tom has recently stated that one third of his patients remain still, one third move a little, and one third move more than is desirable.

taking 12 grains (800 mg.) a day. It is not surprising therefore, when 35 to 40 per cent nitrous oxide is needed for loss of consciousness in the most susceptible patient, that patients who have become tolerant to depressants should barely lose consciousness with twice this amount. Moreover, to render a patient merely unconscious ('stage of delirium'), and to abolish reflex response to surgical stimuli ('stage of surgical anaesthesia'), are very far from the same thing (Macintosh, 1955). The question is: how wide is the gap between these stages?

The answer to this question may be given in terms of the amount by which the strength of an anaesthetic must be increased in order to bridge the gap. Data given by Seevers and Waters (1938) suggest that with cyclopropane an increase of roughly 25 per cent is needed for this purpose; but this is probably too low an estimate. For all other available evidence suggests that depth of anaesthesia is not sensitive to small increments of anaesthetic Haggard (1924d) found that in the dog the amount of ether needed to produce unconsciousness had to be more than doubled before the corneal reflex was abolished. In patients under cyclopropane, to effect a clinically distinguishable deepening of anaesthesia when the stage of surgical anaesthesia has just been entered, the concentration of the gas must be nearly doubled; and to take the next step, which gives abdominal relaxation, it must be nearly doubled again (Seevers and Waters, 1938). Macintosh (1955) has estimated that the amount of anaesthetic that produces unconsciousness must be increased roughly six to eight times before it provides conditions suitable for an abdominal operation. It seems, therefore, that the strength of an anaesthetic must be at least doubled to bridge the gap between mere loss of consciousness and the establishment of satisfactory anaesthesia. It is not surprising, then, that in my investigation very long administrations of nitrous oxide, which brought brain tension nearly into equilibrium with inspired tension, made anaesthesia hardly any deeper than it had been after the induction period, when brain tension was less than 80 per cent of inspired tension. For this represented an increase of only about 25 per cent. Nor is it surprising that increasing the strength of nitrous oxide from 83 to 91 per cent for five minutes had a negligible effect in subjects who had developed a high degree of tolerance and were barely unconscious. Bennett and Seevers (1937) found that the effect of differences of this order was detectable only when they resulted in restriction of oxygen to about 6 per cent, which their experiments suggested was critical for brain function. It is evident, therefore, that extreme tolerance may raise the threshold of anaesthesia far beyond the reach of nitrous oxide; and that even minor degrees of tolerance may make the stage of surgical anaesthesia completely inaccessible with this anaesthetic. It seems open to

question whether the danger of dental gas in "an alcoholic man with a flabby heart", to which Macintosh (1952) has called attention, is to be attributed so much to the state of the patient's myocardium as to the severity with which oxygen has to be restricted to compensate for the almost total ineffectiveness of nitrous oxide in such a patient.

The Field of Usefulness of Nitrous Oxide.—The study reported in this Chapter suggests, nevertheless, that nitrous oxide, given as the sole anaesthetic and with an atmospheric amount of oxygen, has a field of usefulness.

It is suitable only for patients whom it is capable of making completely unconscious. The first requirement, therefore, is to ascertain the patient's habits with regard to depressants. In children it can usually be assumed that no degree of tolerance has been acquired; and in adults who take no depressants it is easy to elicit this fact by asking a few simple questions. The anaesthetic, however, need not always be withheld from those who take depressants, for they may not have developed a high degree of tolerance. If it is desirable to use it in these patients, their response should be tested and the anaesthetic supplemented if necessary.

In suitable patients, nitrous oxide, used by the method described in this Chapter, that is to say, given through a cuffed endotracheal tube introduced after rapid induction with cyclopropane and suxamethonium, and then assisted when necessary by relaxants but not by any analgesic or depressant drug, has considerable advantages. It provides sufficient narcosis for any operation in surgery without risk of anaesthesia ever becoming either too light or too deep; the respiratory centre and other vital functions are but slightly if at all depressed; satisfactory operating conditions, with complete relaxation of all voluntary muscle, can be assured for short or long periods, or periods of unforseeable length, by selecting the appropriate relaxant; and at the end even of a very prolonged administration, recovery of consciousness is rapid—with no other anaesthetic can the anaesthetist be sure of its return in such cases within four or five minutes of the anaesthetic being withdrawn.

These advantages are of special value in obstetrics. Here the main dangers of anaesthesia are, in the mother, vomiting, and in the newborn, asphyxia due to the action of the anaesthetic on the respiratory centre. With the method I have described, vomiting is no longer dangerous once the cuffed tube is in place, and prior to this its danger can be avoided by carrying out induction with the patient on her left side and tilted head downwards; and depression of the respiratory centre in the newborn is entirely avoided. Since 1953 I have used the method with success for delivery by forceps or Caesarean section (Bourne 1956 and 1958). In January, 1955, I described the method to

my colleagues at St. Thomas's Hospital, where it has since become standard practice (Wylie and Churchill-Davidson, 1960*a*).

I have found the method helpful also in dental and other operations in ambulatory patients, when it was desirable to provide fully satisfactory anaesthesia for an indefinite length of time. It would be safe, however, only in the hands of trained anaesthetists equipped with all the appliances needed for major anaesthetic procedures. Under existing arrangements, neither the trained anaesthetists nor the appliances are generally available in dentists' surgeries or outpatient departments. Therefore, the method would not solve the problem of anaesthesia in the mass of ambulatory patients. The solution of this problem calls for an altogether fresh approach.

CONCLUSIONS

Nitrous oxide without supplement or relaxant is too weak for ambulatory work. In susceptible patients—those who have not developed cross-tolerance—it is capable of inducing a state bordering on anaesthesia, but induction may take ten minutes. During this time, even the susceptible patient may become unmanageable as he passes through the stage of delirium; and when induction is completed he may respond to the surgical stimulus if it is one that gives rise to much pain. At any stage he may vomit.

The patient who has developed cross-tolerance cannot be anaesthetised below the stage of delirium and may not even be made completely unconscious. He may experience pain.

In the hands of the experienced anaesthetist, using intubation, relaxants and, when necessary, supplements, nitrous oxide might be put to good use in ambulatory patients. For the 'occasional' anaesthetist it is unsuitable.

Chapter VIII

A FRESH APPROACH TO THE PROBLEM OF GENERAL ANAESTHESIA IN DENTISTRY

In the anaesthesia of ambulatory patients, an important requirement is speed; the anaesthetic should be quick-acting and quickly reversible, particularly in dentistry: "it is an unpardonable offence on the part of the anaesthetist if the patient is not fit enough to vacate the chair and premises at once" (Macintosh, 1952). The anaesthetic should nonetheless be effective, and it is mainly here that the traditional choice of nitrous oxide appears to be at fault.

It used to be thought, and in some quarters perhaps it still is thought, that, quite apart from the question of effectiveness, major operations needed deep anaesthesia with a potent anaesthetic, whereas all that was required for minor surgery was a 'whiff of gas'. If a patient was subjected to a major operation under light anaesthesia, it was supposed, he was liable to become shocked.

This notion was based on three assumptions: that major operations were more painful than minor ones; that bombardment of the central nervous system with pain impulses, if it was intense, was capable of producing shock in the lightly anaesthetised patient; and that deep anaesthesia blocked the pathways of pain and so protected the patient against shock. It now seems probable that all three of these assumptions are false.

In the first place, the sharpest pain is probably that which comes from the surface of the body. There was evidence for this in the tests reported in Chapter VII, in which patients often reacted briskly to the stimulus of incising the skin at the beginning of the operation, or suturing it at the close, but made little or no response during the intermediate stages, even when the operation was a major one. This suggested that the superficial operations of minor surgery might be every bit as painful as major procedures involving deep structures.

Secondly, there appears to be no evidence that anaesthetics block the pathways of pain. The locus of action of morphine, which has been extensively studied, has not yet been finally settled (Goodman and Gilman, 1955*b*); and it seems likely that perception of pain is annulled in anaesthesia simply in consequence of the abolition of consciousness.

Finally, since the introduction of relaxants into the practice of anaesthesia, which allow good operating conditions to be secured by peripheral paralysis even in patients barely unconscious, abundant evidence has accumulated to show that light anaesthesia is not conducive to shock even in the most extensive operations. Gray (1957) noted this absence of shock "in patients only just asleep . . . moving, frowning or showing other reactions to stimuli", and was led to question what was meant by unconsciousness, so light was our anaesthesia nowadays, and to ask whether it was not, after all, only loss of memory from instant to instant.

It is therefore unnecessary on this account to relate depth of anaesthesia to the severity or extent of the operation or to the intensity of the pain it would produce in the conscious patient. No matter how extensive the operation, the patient need be no more than just unconscious.

If the methods used today by trained anaesthetists were open to use by 'occasional' anaesthetists, minor as well as major operations could be performed with patients 'only just asleep' and the whole problem would be simplified. Unfortunately, however, these methods are entirely dependent on the use of relaxants, which would be highly dangerous with anaesthetists of limited experience. The 'occasional' anaesthetist has therefore to rely on the central action of the anaesthetic for the effects he wishes to produce, and these include not merely abolition of consciousness but abolition of reflex response to pain. The depth of his anaesthesia, therefore, unlike that of the trained anaesthetist, continues to be related to the intensity of pain. It is important to realise what this means

Its implication will be understood by any physician who has had charge of a patient in coma. To assess the depth of coma, he applies a stimulus; if there is no response, he tries a more painful one; if there continues to be no response even when the stimulus is one that would cause considerable pain, he recognises that the coma is deep. If the coma was due to narcotic poisoning, he might regard the patient's condition as grave. It is precisely this state that the 'occasional' anaesthetist must induce if operating conditions are to be satisfactory. Depression of the central nervous system to this level can hardly be regarded as minor anaesthesia

Thus the traditional view that deep anaesthesia is needed for major operations and light anaesthesia for minor ones is fallacious. The truth is, in fact, the opposite. For a minor operation on the hand, for example, or for a difficult tooth extraction, the 'occasional' anaesthetist may need to induce a deeper level of anaesthesia than would nowadays be used by trained anaesthetists for such major operations as removal of stomach or lung. Moreover, the 'occasional' anaesthetist

is expected to accomplish this in little more than a minute, and to ensure recovery within the same short space of time. He is unlikely to succeed unless he has access to an anaesthetic a good deal more powerful than nitrous oxide.

Macintosh (1952) believes that it is virtually impossible to meet the requirements of dental anaesthesia with any anaesthetic, "using the word 'anaesthetic' as it should be used—an agent to keep the patient unconscious, quiet and pink throughout the operation." He believes it can be done only by the use of controlled hypoxia: "there is one condition, however, which gives rise to sudden unconsciousness, leads rapidly to a state approaching death, and yet can be reversed almost equally rapidly so that the patient recovers quickly, and there are negligible after-effects. I refer to acute asphyxia—that is depriving the patient abruptly of oxygen as by giving him some other gas to breathe for a limited time".

I question the validity of these conclusions and in this Chapter explore the possibility of developing a method that would meet the requirements without having recourse to hypoxia. Intravenous anaesthesia will be considered first.

INTRAVENOUS ANAESTHESIA

For practical purposes, intravenous anaesthesia may be taken as meaning anaesthesia with thiopentone; for although many different barbiturates and drugs of other kinds have been tried, thiopentone remains without a rival.

Probably most anaesthetists believe that this anaesthetic would be unsuitable for general use in ambulatory patients and would be dangerous in the hands of the 'occasional' anaesthetist; they would be unanimous in condemning its use (or, in fact, the use of any anaesthetic) by the operator acting as his own anaesthetist: "the safeguarding of an unconscious patient is a wholetime responsibility" (Macintosh and Bannister, 1952*j*). Nevertheless, the use of thiopentone in dentistry has been advocated, and by no one more insistently than by Drummond-Jackson, a dental surgeon. He claims that it compares favourably for safety, not only with inhalational but also with local anaesthetics, and in his view its properties make it specially suitable for use by the operator-anaesthetist. Condemnation of its use by the operator-anaesthetist, he believes, is misguided and reflects only ignorance, conservatism and bias (Drummond-Jackson, 1952*a*).

Drummond-Jackson states that he has used intravenous anaesthesia continuously for 20 years and given it to 20,000 patients sitting up in the dental chair without a death or serious sequel (Drummond-

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body-weight. Using a 5 per cent solution, he finds that adults require about 0·5 ml. per 10 pounds body-weight (5·5 mg./Kilo), but that for children it is necessary to add 1 to 2 ml. (50 to 100 mg.) to the dose calculated in this way. Thus an adult weighing 10 stone (140 pounds; 64 Kilos) would need about 7 ml.; a child weighing 50 pounds (23 Kilos), 3·5 to 4·5 ml. In the study reported here, these doses were used, the children being given the lower of the doses mentioned.

Material and Methods

Seventeen patients about to undergo relatively trivial operations on the nose or throat were used for the study. Ten were female. Apart from the local condition they were healthy. Three were children under ten years of age, five were in their second decade and nine were adults, most of them young. For pre-anaesthetic medication they were given scopolamine gr. 1/150 (0·4 mg.) or half this dose if they weighed less than 75 pounds (34 Kilos).

The study was made with the patient supine. The dose of thiopentone was injected after the patient had been breathing oxygen through a face mask from a closed reservoir for periods up to or a little more than a minute. In seven subjects carbon dioxide was absorbed with soda-lime, but in the remainder it was allowed to accumulate. Respirations were recorded with a Benedict spirometer.

In six subjects suxamethonium was given three or four minutes after the thiopentone so that the pattern of respiratory arrest with thiopentone could be compared with that resulting from peripheral paralysis of the respiratory muscles.

Results

In all but one of the subjects, the injection of thiopentone was followed by respiratory arrest. Its duration was from half a minute to one and three-quarter minutes. In eleven subjects it lasted a minute or longer. In the subject whose respiration was not arrested, tidal volume was very much reduced. Typical results are shown in Fig. 10.

Discussion

Scopolamine, given here to lessen secretions in the mouth and pharynx and for its mild sedative effect, stimulates rather than depresses respiration and tends to counteract the respiratory depressant effect of barbiturates (Goodman and Gilman, 1955*c*). The arrest of respiration observed in this study, therefore, cannot be attributed even in part to the premedication. Nor was it due to breath holding, which sometimes interrupts respiration during induction with cyclopropane; for this gives a totally different pattern in the

Jackson, 1952*b*). In two cases, however, he encountered a potentially dangerous emergency, which appears to have taken the form of respiratory arrest with an "advanced state of collapse", necessitating artificial respiration by the mouth-to-mouth method (Drummond-Jackson, 1952*c*). Nevertheless, he believes that the depression of respiration that occurs with thiopentone is usually slight and of little clinical importance, and "the occasional cessation" of respiration of no moment if promptly treated (Drummond-Jackson, 1952*d*). Another complication that he met from time to time was laryngeal spasm; but this, also, he regards as not dangerous, and he believes its incidence could be kept down to one case in a thousand with proper care (Drummond-Jackson, 1952*e*).

It is mainly through his denial that respiratory depression and laryngeal spasm are potential dangers with thiopentone that Drummond-Jackson finds himself in disagreement with anaesthetists For they believe that the safety of an anaesthetic, particularly in the hands of the 'occasional' anaesthetist, depends on the extent to which it spares the respiratory centre. An anaesthetic that leaves the respiratory centre active when it has abolished response to pain and other reflexes they consider to be a great deal safer than one that may arrest respiration before a satisfactory level of anaesthesia has been reached; and they believe thiopentone to be an anaesthetic of the latter kind. Furthermore, it appears to them to have a special tendency to provoke dangerous laryngeal spasm.

To some extent this difference of opinion might be explained by the fact that Drummond-Jackson's method of using thiopentone is not strictly comparable with that used in general surgical practice, on which the views of anaesthetists are based. In general surgery, the administration of thiopentone is nearly always preceded by medication with a respiratory depressant such as papaveretum; and the dose of thiopentone is not restricted by the need for early ambulation. Drummond-Jackson uses no premedication, and is careful to give as little thiopentone as possible so as to minimise the time of recovery. Given in this way, the anaesthetic might not depress respiration so dangerously as anaesthetists are led to expect from their experience. To reject his claims, therefore, without investigating his method, as some have been inclined to do, seems unjustified, particularly in view of the fact that his experience with the anaesthetic in dental practice probably exceeds that of any other person in this country. These considerations prompted me to study the respiratory effects of the anaesthetic used in the way he recommends.

Effect of Thiopentone on Respiration.—Drummond-Jackson's wide experience has enabled him roughly to define the dose of thiopentone that is needed in dentistry in terms of the patient's

spirometer-tracing (Chapter X). With thiopentone, respiration stopped with the thorax in the position of relaxation, as when the respiratory muscles were paralysed with suxamethonium. The arrest can only have been due to depression of the respiratory centre.

The high incidence of respiratory arrest in the small series of patients studied suggests that this complication would frequently occur in dental practice even if the dose of thiopentone was always carefully regulated. There is no certainty, however, that this would be done. It is unlikely that dentists would weigh their patients; guess work would come in; and weight is not an infallible guide. Drummond-Jackson found considerable individual variation in patients' requirements, which could be estimated only with experience. Some patients, therefore, would inevitably be overdosed, and this might result in dangerously prolonged apnoea. Moreover, apnoea is not the only danger; laryngeal spasm has also to be considered.

The tendency of thiopentone to cause laryngeal spasm has never been satisfactorily explained. It is often said that thiopentone sensitises the larynx; but it is doubtful if this has any meaning. A better understanding of this complication might help in evaluating the risk of meeting with it in dentistry. In my view, its underlying cause with any anaesthetic is depression of the respiratory centre. My reasons for this belief are as follows.

The larynx was evolved, not as an organ of phonation, but as a protective sphincter, of vital importance to the pulmonary air tract (Negus, 1949*a*). The sphincteric muscles are of more ancient origin than their antagonists, the dilators (Negus, 1949*b*). As a result of its primitive origin and importance, the sphincteric function is retained when other functions of the larynx are lost (Negus, 1949*a*). This predominance of the sphincteric function, to which Negus has thus drawn attention, is seen in ordinary life when a person chokes. When this happens, the need to protect the lungs at first is paramount. The larynx shuts tightly and breathing is impossible. Respiration, however, is also a primitive and vital function: the subject struggles for breath Under these conditions, carbon dioxide rapidly accumulates; and since the respiratory centre is fully active, the demand for the larynx to open and admit air soon grows to be as urgent as the demand for the larynx to remain shut, whereupon the sphincteric action is partially overcome. Thus the larynx may be regarded as an organ that is under the control of two opposing nervous mechanisms, both of them primitive and vital, the sphincteric one dormant except at need. When it is aroused, the two mechanisms find themselves competing for the control of the larynx. It is easy to see that if either one is depressed, the other holds the field.

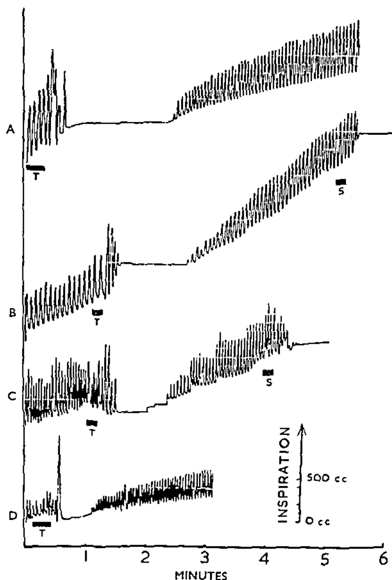


FIG 10—Effect of thiopentone (T) on respiration in four patients anaesthetised with the dose recommended by Drummond-Jackson In two patients the effect of suxamethonium (S) is also shown A, woman, aged 27, weight 132 pounds (60 Kilos), B, woman, aged 40, weight 138 pounds (64 Kilos), C, youth, age 17, weight 145 pounds (66 Kilos); D, girl, age 8, weight 56 pounds (25 Kilos)

or from a combination of both these effects, would make the use of thiopentone in dentistry dangerous unless certain precautions were taken.

One of these precautions is simple and could easily be taken by 'occasional' anaesthetists in dentists' surgeries: the administration of oxygen, perhaps with small amounts of carbon dioxide, for a minute or so before the anaesthetic is given and continued until anaesthesia is established. By providing a reserve of oxygen in the lungs, this would greatly delay the onset of hypoxia should spasm occur. Even so, for complete safety the anaesthetist should be equipped with all the apparatus needed for dealing with respiratory emergencies, and this could be used effectively only by trained hands. Probably, therefore, if danger is to be avoided, the anaesthetic should be used only by trained anaesthetists.

Nevertheless thiopentone has considerable advantages: induction is rapid; the most 'resistant' patient is easily brought under control; the sensation of losing consciousness with the anaesthetic closely resembles that of falling asleep; and there is no post-anaesthetic nausea. From the patient's point of view, the anaesthetic has no rival. Therefore, in selected cases and in experienced hands, such as those of Drummond-Jackson, the anaesthetic has a place in dentistry. Recovery, however, is slow, and this alone would prevent its widespread use. For a solution of the problem, therefore, we must turn to inhalational methods.

INHALATIONAL ANAESTHESIA

In Chapter VII, attention was drawn to the fact that, with an inhalational anaesthetic, depth of anaesthesia is governed by the tension of the anaesthetic in the brain, and the rate of induction and recovery is governed by the rate of change of this brain tension. The problem, therefore, of obtaining anaesthesia of satisfactory depth, yet with rapid induction and recovery, calls for consideration of the factors governing inert gas exchange in the body; for, physically and chemically, the gaseous and volatile anaesthetics behave in the body as inert gases.

Inert Gas Exchange.—The factors governing the uptake and elimination of inert gases have been comprehensively reviewed by Kety (1951) in an account that includes his own very considerable contributions to this field of knowledge. It is mainly on this review, and on a simplified account by the same author (Kety, 1950*b*), that I have based the discussion that follows; but I have also drawn on earlier work by Haggard (1924*a*, *b*, *c*, *d* and *e*), to whom Kety himself pays tribute and whose study of ether exchange in the dog was exemplary.

Some anaesthetics have the property of depressing the sphincteric control of the larynx more than they do the respiratory centre. Ether and cyclopropane are examples. With either of these agents, a level of anaesthesia can be reached at which the sphincteric reflex is completely abolished while breathing remains active. It is at this level that it becomes possible to intubate the larynx. With these anaesthetics, laryngeal spasm would, in my view, seldom if ever be a danger were it not for the practice of using with them, either as pre-anaesthetic medication or for induction, drugs that are strong respiratory depressants. With thiopentone, however, it is quite another matter.

This anaesthetic has precisely the opposite effect on the central control of the larynx to that of ether or cyclopropane. It depresses *the respiratory centre far more intensely than it does the sphincteric* nervous mechanism, so that even with doses much above those which arrest respiration, the sphincteric action remains strongly active. If, after such doses, an attempt is made to intubate the larynx, the most intense and prolonged laryngeal spasm may follow. The respiratory centre being out of action, the sphincteric mechanism is unopposed. The patient makes no attempt to breathe. His larynx remains tightly shut and he becomes severely asphyxiated.

Experience with thiopentone as an anaesthetic for bronchoscopy is consistent with this explanation of laryngeal spasm. When thiopentone first came into use, it seemed to offer a solution to the problem of providing general anaesthesia for this procedure. Its use for this purpose, however, was found to be precluded by the activity of the sphincteric reflex. Two ways out of the difficulty were found. The first was to deaden the sphincteric reflex by making a preliminary application of local anaesthetic to the surface of the larynx. The second was to administer 10 per cent carbon dioxide in oxygen during the administration of thiopentone, and again before withdrawing the bronchoscope (Fatti and Morton, 1944). The success of these measures may be explained by the fact that each in its own way adjusted the balance between the two competing nervous mechanisms in a direction that favoured the respiratory one.

If this explanation of laryngeal spasm is correct, it follows that this complication should be expected whenever the sphincteric reflex is evoked in the presence of respiratory depression. If this is so, laryngeal spasm should be regarded as an ever present danger with thiopentone in dentistry. For not only is the dose needed in dentistry [illegible]

that the risk of asphyxia either from apnoea, from laryngeal spasm,

tail represents the more gradual process of tissue saturation. The knee marks the point at which lung-washout gives place to tissue-saturation as the dominant influence.

Many physiological variables affect the shape of the curve obtained with any given gas. These include: minute volume of respiration; lung volume; cardiac output; blood flow to muscle and fat; and the total mass of these tissues, for they constitute the main gas-absorbing bulk of the body. The effect of these factors, however, is small compared with that of a single physical property of the gas itself: the gas's solubility in blood. This determines the height of the knee in the alveolar uptake curve; and since the blood-solubilities of gases, including those used in anaesthesia, vary widely, the height of the knee varies to a corresponding extent when the different gases are administered in turn to a given individual with uniform values for all the physiological variables. With a gas of low blood-solubility the knee is high; with one of high blood-solubility the knee is low. The reason for this will become apparent if we consider the hypothetical extremes of solubility.

Effect of Blood-Solubility on Alveolar Uptake Curve.—A totally insoluble gas would not diffuse into the pulmonary blood stream and be carried away to the tissues; there would be no loss from the lungs. If such a gas were given at a constant inspired tension, its alveolar tension would increase exponentially as lung-washout proceeded until, after about three minutes, alveolar tension equalled inspired tension. The curve obtained would be all initial rise and no tail.

A gas of extremely low blood-solubility would give an almost identical curve. The loss by diffusion into the pulmonary blood of only a tiny fraction of the amount contained in the lungs at any one moment would bring the blood tension of the gas into equilibrium with its tension in the alveoli. The capacity of the blood for such a gas would be extremely small. Likewise, the capacity of the entire body (leaving adipose tissue out of account for the moment) would also be extremely small, for, with the sole exception of adipose tissue, the tissue: blood partition coefficients of gases are close to unity. With a gas of extremely low blood-solubility, therefore, the initial rise of the alveolar tension curve would reach nearly to the top in Fig. 11, and the tail would lie only just below the line denoting equilibrium with inspired tension. In short, alveolar tension and inspired tension would be almost completely equilibrated within about three minutes.

At the other extreme would be a gas whose solubility in blood was very nearly infinite. Here, all but a tiny fraction of the amount in the lungs at any one moment would diffuse into the blood; and since in healthy lungs diffusion is virtually instantaneous, the gas would

"When an inert gas," states Kety (1951), "is abruptly introduced at a constant partial pressure into the inspired air, the tissues of the body do not suddenly acquire the gas at this partial pressure. A number of physical processes intervene, each with its own time rate of change, to delay the eventual saturation of the tissues. First, by means of pulmonary ventilation the gas is inspired, diluted with the functional residual air and distributed to the alveolar membrane. Here diffusion occurs and alveolar gas is equilibrated with pulmonary blood which is then distributed via the peripheral arteries to the individual tissues. A second diffusion step now occurs across the

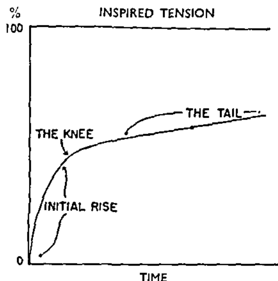


FIG 11. — Characteristic curve of alveolar (or arterial) tension of any inert gas breathed at a constant inspired tension. (Modified from Kety, 1950*b*)

capillary membrane, interstitial fluid and cellular membrane and through the intracellular fluid itself. The venous blood from all the tissues returns to the lungs carrying some fraction of its original gas concentration which is thus contributed to the equilibration process occurring at the alveoli. In this manner the alveolar, arterial, tissue and venous tensions of the inert gas in question gradually rise toward eventual equilibrium with the tension inspired."

As this complex process of equilibration proceeds, the tension of the gas in alveolar air increases continuously, but not at a uniform rate. Plotted against time, alveolar tension rises in a curve that, in its general characteristics, is the same for every inert gas (Fig. 11). The curve has, in Kety's terminology: an initial rise, which is steep and occupies three minutes or less; a knee; and a tail, which slopes gradually upwards until, after several hours, complete equilibrium with the inspired tension is reached. The steep initial rise represents the phase in which lung-washout predominates. The slowly rising

tail represents the more gradual process of tissue saturation. The knee marks the point at which lung-washout gives place to tissue-saturation as the dominant influence.

Many physiological variables affect the shape of the curve obtained with any given gas. These include: minute volume of respiration; lung volume; cardiac output; blood flow to muscle and fat; and the total mass of these tissues, for they constitute the main gas-absorbing bulk of the body. The effect of these factors, however, is small compared with that of a single physical property of the gas itself: the gas's solubility in blood. This determines the height of the knee in the alveolar uptake curve; and since the blood-solubilities of gases, including those used in anaesthesia, vary widely, the height of the knee varies to a corresponding extent when the different gases are administered in turn to a given individual with uniform values for all the physiological variables. With a gas of low blood-solubility the knee is high; with one of high blood-solubility the knee is low. The reason for this will become apparent if we consider the hypothetical extremes of solubility.

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be almost entirely swept away by the blood stream the moment it reached the alveoli. The capacity of the blood and body tissues for such a gas would be enormous. The initial rise of its alveolar tension curve would be insignificant; the knee would be practically on the base line; and the approach towards equilibrium would be gradual throughout. The curve would be nearly all tail and no initial rise. After three minutes alveolar tension would be almost zero.

Ranged between these hypothetical extremes lie the volatile and gaseous anaesthetics. Their solubilities in water, blood, tissues and oil (where such values have been determined), together with the

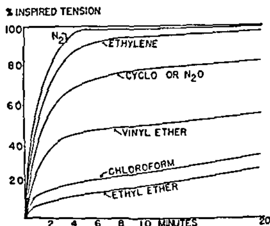


FIG. 12.—Effect of blood-solubility on alveolar (or arterial) uptake of different gases inspired at constant tensions. (Kety, 1950*b*).

solubilities of nitrogen and acetone, are given in Table IV, in which the gases are listed in order of increasing solubility in blood. The effect of the different blood-solubilities of some of these gases on the alveolar tension curve is shown in Fig. 12.

So far, only alveolar tension has been considered. It is, however, with tissue tension, and particularly brain tension, that the anaesthetist is concerned. In healthy lungs, diffusion from the alveoli into the blood is, as already stated, virtually instantaneous. This means that the tension of a gas in the blood leaving the pulmonary capillaries, that is to say in arterial blood, may for practical purposes be regarded as identical with its tension in the alveoli. In Fig. 12, therefore, the curves represent not only alveolar but also arterial tension. Arterial tension, however, represents tissue tension only when the entire body has become fully saturated, a process taking several hours. During this process, and again during the process of elimination of the gas after the administration has been stopped, the tension in any given tissue is represented, not by arterial tension, but by that of its venous blood. This lags behind arterial tension to an extent that, in any tissue other than adipose (in which differences of

TABLE IV*

OSTWALD SOLUBILITY (OR PARTITION) COEFFICIENTS AT 37°–38°C

Gas	*Water/Gas*	*Blood/Gas*	*Tissue/Blood*	*Oil/Water*
Nitrogen	0·01	0·01	brain 1·1, liver 1·1, fat 5·2	5·2
Ethylene	0·09	0·14	brain 1·2, heart 1·0	14·4
Cyclopropane	0·20	0·46		35·0
Nitrous oxide	0·44	0·47	brain 1·0, heart 1·0	3·2
Ethyl chloride	1·2	Pig 2·3, Cow 1·6		
Divinyl ether† ('Vinesthene', 'Vinethene')	1·32			41·3
Halothane ('Fluothane')		3·6		330
Chloroform	4·6	7·3	brain 1·0, liver 0·9	110‡
Trichloroethylene ('Trilene', 'Trimar')	1·6	9·0		(15 at 20°C)
Diethyl ether (Ether)	15·5	15·0	brain 1·14	3·2
Acetone		333·0		0·2

solubility play an important part), depends mainly on the tissue's blood supply. With organs that are richly supplied with blood, such as the brain or heart, the lag is small, as was seen in Fig. 7. The curves shown in Fig. 12, therefore, may be regarded as representing roughly the rates of increase in brain tension. Likewise, the rates of elimination from the brain would be represented, again roughly, by the same curves inverted. This approximation is sufficient for pur-

* For sources of data see Kety (1951) except for the following (sources in parenthesis) Ethyl chloride (Nicloux and Scotti-Foglieni, 1928); Halothane (in blood Bourne, 1957*a*; in oil: Raventós, 1956); Trichloroethylene (Powell, 1947), Acetone in oil (Ruigh, 1939).

† The blood-solubility of divinyl ether does not appear to have been measured; its correct position in the Table is therefore uncertain

‡ This value may represent a misprint in Kety's review; other authorities give 100.

be almost entirely swept away by the blood stream the moment it reached the alveoli. The capacity of the blood and body tissues for such a gas would be enormous. The initial rise of its alveolar tension curve would be insignificant; the knee would be practically on the base line; and the approach towards equilibrium would be gradual throughout. The curve would be nearly all tail and no initial rise. After three minutes alveolar tension would be almost zero.

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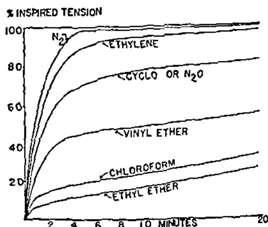


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incompletely saturated), elimination of the more soluble anaesthetics must take its time and will inevitably be slow.

Effect of Fat-Solubility on Speed of Induction and Recovery.—The buffering effect of high blood-solubility will be intensified if the anaesthetic has also a high fat-solubility. The curves in Fig. 12 were constructed by Kety from calculated not measured data, and the effect of fat-solubility, which influences the slope of the tail, was intentionally omitted. Had it been included, the curve for ether would have overtaken that for chloroform, since, of the two anaesthetics, chloroform is much the more soluble in fat. Halothane, which is not represented in Fig. 12, would have a curve whose tail approached the level of full saturation extremely slowly, since this anaesthetic's fat-solubility is exceptionally high. To get the full effect of any given inspired tension of halothane would therefore take a great many hours, and an equally long period would then be required for complete elimination of the anaesthetic. Owing to the poor blood supply of adipose tissue, however, the effect of high fat-solubility becomes marked only in prolonged administrations and is probably of little importance as a factor delaying induction and recovery in the brief administrations that are needed in work with ambulatory patients. Here, the controlling influence is the anaesthetic's solubility in blood. If both induction and recovery are to be rapid, this must be low.

Influence of Blood-Solubility on the Safety of an Anaesthetic.—Blood-solubility, however, is important not merely as a factor influencing speed of induction and recovery. It has wider implications. For, since it determines (inversely) the extent to which tissue tension keeps pace with alterations in inspired tension, blood-solubility influences an anaesthetic's safety. With a highly soluble agent like ether, no sudden change in tissue tension is possible. This means that if a gross overdose is inadvertently given, the anaesthetist has ample time to observe the signs of deepening anaesthesia and reduce the strength of the mixture. With an anaesthetic of low blood-solubility, however, increase in tissue tension follows hard on the heels of increase in inspired tension; anaesthesia may deepen very rapidly, and a gross overdose might be almost instantly fatal. It is therefore important with the less soluble anaesthetics to consider the factors that favour the giving of an overdose, chief of which are volatility and potency

Volatility governs the potential strength of the inspired mixture. The more volatile the anaesthetic, the greater is the risk of its being given at a high inspired tension. An anaesthetic gas, or a volatile agent that boils at less than room temperature, might be given at a strength of a hundred volumes per cent, whereas an agent whose

poses of the present discussion; but it should be borne in mind that true values for brain tension would give curves that sloped less steeply during the first ten minutes of uptake or elimination. After this interval, cerebral and arterial tensions are almost identical (Schmidt, 1950).

Effect of Blood-Solubility on Speed of Induction and Recovery.—It will be seen from Fig. 12, that with a gas of low blood-solubility any alteration in inspired tension is quickly reflected in the brain, but with one of high blood-solubility there is a considerable delay, the whole body acting as an enormous buffer (Haggard, 1924*c*) It follows that, with an inhalational anaesthetic, speed of induction and recovery is governed by the anaesthetic's solubility in blood. Low blood-solubility favours rapid induction and recovery, whereas with anaesthetics of high blood-solubility, such as trichloroethylene or ether, induction and recovery are slow.

Delay in induction due to high blood-solubility can, to some extent, be overcome. If ether, for example, were administered from the outset at the concentration that gave a satisfactory depth of anaesthesia when full equilibrium had been reached, induction would take several hours; and it would be a long time before the patient even lost consciousness. Anaesthetists get over this difficulty by starting the administration, not with this, but with a much higher concentration, which, if continued indefinitely, would kill the patient. Then, as the desired level of anaesthesia is approached, they decrease the concentration (Kety, 1950*b*) Even so, induction with this very soluble anaesthetic is slow. Haggard, who found that in dogs ether brain tensions of 3 per cent gave light or moderate anaesthesia, and 4 per cent, deep anaesthesia, had to administer the anaesthetic for about twenty minutes at more than five times these concentrations before these brain tensions were reached (Haggard, 1924*d*). With chloroform, which has only half the blood-solubility of ether and is effective at even lower brain tensions than is ether, induction can be accelerated by using very high concentrations to give anaesthesia within a minute. Simpson, the discoverer of this anaesthetic, obtained complete insensibility with it in six or seven breaths (*Brit. J. Anaesth.*, 1958), though to get such a rapid effect he may well have given the anaesthetic at ten or more times a concentration that would have been lethal if continued. It is in fact standard practice with all the inhalational anaesthetics to accelerate induction in this way. Recovery, however, is not open to the same treatment. For, when the anaesthetic is withdrawn, its inspired tension cannot be reduced below zero. And although the full effect of the buffering action of the body will not be seen after accelerated inductions and brief administrations (since tissues with a poor blood supply will then be only very

each be given careful and separate consideration if the action and potentialities of an anaesthetic are to be fully understood. Low blood-solubility might make an anaesthetic very dangerous if the anaesthetic happened also to be highly volatile and very potent.

The importance of blood-solubility has been overlooked. The blood-solubility of divinyl ether, which has been widely used for more than a quarter of a century, appears never to have been determined. And the new anaesthetic, halothane, had been extensively investigated and had passed into widespread clinical trial before ever its blood-solubility had been measured (Bourne, 1957*a*). Yet with knowledge of this constant, much could have been foreseen. If its blood-solubility had been considered in conjunction with its volatility and potency, the latter of which could have been accurately determined in animals by following the lines of Haggard's experiments, both the flexibility of anaesthesia with halothane and the potential danger of the anaesthetic could have been forecast, and the hazard of clinical trial greatly reduced. Search is now being made for new anaesthetics. If one were found with precisely the same properties as halothane, except for its having the very low blood-solubility of nitrogen, it might be lethal in a few breaths if given at much above its therapeutic concentration: if it were given at the same lethal concentration, but had the very high blood-solubility of acetone, the anaesthetist might at first despair of ever getting the patient to sleep.

Thus, low blood-solubility, though a prime requisite if an anaesthetic is to be suitable for work with ambulatory patients, should be combined with a potency that is not too great, if the anaesthetic is to be safe. And this is particularly necessary if the anaesthetic is a gas or a liquid of high volatility.

It is not surprising, since low blood-solubility is the property that makes anaesthesia flexible, that the anaesthetics that have been found to be of use in ambulatory work are among those with low blood-solubilities. Up to the present time the selection of anaesthetics for this work has been entirely empirical. It may now be placed on a rational basis. If we are to improve our methods in this field it is amongst substances with low blood-solubility that we must look for fresh anaesthetics, whether at present existing or as yet undiscovered.

In Table V, I have listed the inhalational anaesthetics with their blood-solubilities, boiling points and potencies, using such data as are available. In the column headed "Equipotent Concentrations" I have given the inspired tensions that, at full equilibrium, would in my opinion have equal effect. In the column headed "Relative Potency" I have used these values to express the potency of the different anaesthetics as a factor of the potency of nitrous oxide.

boiling point is scarcely any lower than that of water cannot ordinarily be given at a high concentration. Gaseous anaesthetics and liquid anaesthetics with very low boiling points are therefore potentially dangerous, though the danger with a gas is to some extent mitigated by the fact that gases are delivered through flowmeters, which gives the anaesthetist an accuracy of control not possible with volatile liquids except with special apparatus.

Potency determines the magnitude of the possible overdose. With a very weak anaesthetic, such as nitrous oxide, overdose is impos-
[illegible] could be given at

at, say, one volume per cent would constitute a hundred times a therapeutic dose. High potency, therefore, introduces the possibility of gross overdose. This, perhaps, is self-evident; but insufficient attention has been paid to the precise meaning and measurement of potency.

The potency of an inhalational anaesthetic can be satisfactorily expressed only in terms of the brain tension needed to produce a certain, specified and definable depth of anaesthesia. Potency is therefore a difficult value to determine. For, with all the inhalational anaesthetics, full equilibration of inspired tension with brain tension takes several hours. Estimates based on measurements of inspired, alveolar or arterial tensions after administrations that do not allow sufficient time for full equilibration would be misleading, since none of them would then represent brain tension. A way out of the difficulty would be to use the procedure adopted by Haggard and estimate brain tension at any moment during the administration by sampling internal jugular blood Goodman and Gilman (1955*d*) state that this is the only index to the degree of saturation of the brain. This would be possible only in volunteers. Furthermore, to get uniform results, only subjects who have developed no tolerance to central nervous system depressants should be used. As already stated in Chapter VII, no study embodying these principles appears to have been made in man. Consequently, current notions of the potency of the different anaesthetics are at best imprecise, and in one or two instances, totally incorrect. Cyclopropane, for example, is considered very potent because it induces anaesthesia rapidly, when in fact its speed of action is due mainly to low blood-solubility. Trichloroethylene is considered weak because administrations of ordinary length result in no very profound effect, whereas it may in fact be the most powerful of all anaesthetics, the shallowness of effect in the time allowed being due to its low volatility and high blood-solubility. Thus potency, volatility and blood-solubility should

4. An anaesthetic of low blood-solubility, to be safe, should not be too potent.
5. An anaesthetic of low blood-solubility and high potency might be extremely dangerous unless its inspired concentration was strictly limited, either by virtue of its having low volatility, or by its being administered from special dosimetric apparatus.

Review of Existing Anaesthetics

In the light of these conclusions, existing inhalational anaesthetics may now be reviewed with regard to their suitability for use in ambulatory patients. Three of them—nitrous oxide, ethyl chloride and divinyl ether—have been widely used in this field for many years in the United Kingdom, and ethylene was given an extensive trail in America. These anaesthetics, therefore, will be considered first.

Nitrous Oxide

The potentialities of this anaesthetic were reviewed in Chapter VII. Its low blood-solubility ensures a rapid increase in brain tension; but because of its low potency, a state approaching surgical anaesthesia is reached only after it has been administered for a sufficient length of time for brain tension to approximate closely to the maximum permissible inspired tension, and then only in selected patients. Induction therefore takes many minutes and in a considerable proportion of patients must altogether fail. Nitrous oxide is too weak for work with ambulatory patients.

Ethylene

Ethylene is a gas that was introduced as an anaesthetic in 1923. It is ignitable in air and explosive when the mixture is enriched with oxygen. It has the lowest blood-solubility of all the inhalational anaesthetics, and therefore uptake and elimination are faster than with any other anaesthetic. Its potency is generally held to be slightly greater than that of nitrous oxide; Adriani (1952*a*) gives 60 volumes per cent as the concentration needed for loss of consciousness, as compared with 35–70 volumes per cent of nitrous oxide (Adriani, 1952*b*); and Seevers *et al.* (1937) found that 25–35 volumes per cent of ethylene had about the same analgesic effect as 35–40 volumes per cent of nitrous oxide. However, Seevers and his colleagues, and perhaps Adriani also, made their comparison after administrations lasting only ten minutes, when the lower solubility of ethylene would give it an advantage over nitrous oxide. After this interval, the brain tension of ethylene would have reached more than 90 per cent of inspired tension, whereas with nitrous oxide it would not have reached 80 per cent. This would be sufficient to account for the

The values given in these two columns are of necessity highly conjectural and cannot do more than indicate very roughly the order of potency of each anaesthetic. As in Table IV, the anaesthetics are listed in order of increasing blood-solubility.

TABLE V

BLOOD-SOLUBILITY, VOLATILITY AND POTENCY OF THE INHALATIONAL ANAESTHETICS

Anaesthetic	*Blood-solubility* $\left(\frac{Blood}{Gas}\right)$	*Volatility (B.P. °C)*	*Equipotent Concentrations (Vols. per cent inspired tension)*	*Relative Potency* (N_2O = 1)
Ethylene .	0·14	−104	?<80	?>1
Cyclopropane .	0·46	− 34	10	8
Nitrous oxide .	0·47	− 89	80	1
Ethyl chloride	2·0	13	2	40
Divinyl ether ('Vinesthene', 'Vinethene')	2·0*	28	4	20
Halothane ('Fluothane')	3·6	50	1	80
Chloroform .	7·3	61	0·8	100
Trichloro-ethylene ('Trilene', 'Trimar')	9·0	87	0·5	160
Diethyl ether . (Ether)	15·0	35	2	40

* The value given is a rough approximation suggested by the anaesthetic's solubility in water.

CONCLUSIONS

At this point, the conclusions reached so far in the discussion may be summarised as follows.

1. Anaesthesia for minor operations in ambulatory patients sometimes needs to be deeper than that used for major operations.
2. Intravenous anaesthesia would be neither safe nor suitable for general use in ambulatory work.
3. An inhalational anaesthetic, if it is to give the necessary speed of induction and recovery, should have low blood-solubility.

Thus, ethyl chloride combines low blood-solubility with high volatility and high potency—a triad of properties that allows lethal tissue tensions to develop with dangerous speed unless the anaesthetic's vapour strength is strictly limited by special apparatus; and for ethyl chloride no such apparatus has been devised.

Apart from the danger of overdose, however, ethyl chloride is believed to have dangerous cardiac effects. It appears to share with chloroform (and perhaps also the other halogenated anaesthetics, trichloroethylene and halothane) the power of depressing or even arresting the heart at concentrations that arrest respiration and are not much above those needed for satisfactory anaesthesia.

In addition, ethyl chloride is ignitable in air and, within its anaesthetic range, forms explosive mixtures with oxygen or nitrous oxide.

All in all, teaching hospitals seem justified in discarding this anaesthetic as dangerous, and perhaps their example should be followed elsewhere.

Divinyl Ether

This anaesthetic, introduced in 1930, is widely used in ambulatory work, particularly in children. Its blood-solubility does not appear to have been measured but is probably low, as is suggested by its low water-solubility and by the fact that, with it, induction and recovery are rapid.

The potency of divinyl ether is given by Goodman and Gilman (1955*f*) as seven times that of ether, and they state that it is so powerful and produces deep anaesthesia so rapidly that a dangerous plane may easily be entered. This estimate of its potency, however, was based on the blood levels needed for anaesthesia, and reflects low blood-solubility rather than high potency. In terms of vapour strength (or the much more definitive value, brain tension), divinyl ether would almost certainly be found to be no more and perhaps [illegible] lity allows [illegible] h potency [illegible]

However, the danger of overdose with divinyl ether is less than with ethyl chloride, because it is both less volatile and less potent than that anaesthetic. Nor does it seem to have dangerous effects on cardiac activity at concentrations close to those used clinically, as appears to be the case with the halogenated anaesthetics. For these reasons the anaesthetic is undoubtedly safer than ethyl chloride, a fact that has been established in actual clinical practice (Dawkins, 1958).

At the present time in this country, the standard method of administering divinyl ether is from an Oxford Inhaler. This is a

differences observed. It is therefore doubtful whether ethylene is more powerful than nitrous oxide; and although its lower blood-solubility gives it a slight clinical advantage, this is too small to be of practical value. This fact, and its ignitability, which resulted in explosions in America, caused it to be abandoned after a brief trial in the United Kingdom, where it is now unobtainable.

Ethyl Chloride

The anaesthetic properties of ethyl chloride were discovered as long ago as 1847, but it was not widely used until interest in it was revived at the end of the century. Since then it has been extensively used in ambulatory patients. At the present time it continues to be widely used in dentists' surgeries and school dental clinics, but in many teaching hospitals it has been abandoned on account of its danger. This danger is in part the direct outcome of its potency and physical properties.

The potency of ethyl chloride is very high. Goodman and Gilman (1955*e*) state that surgical anaesthesia is maintained by 4 volumes per cent; and 6 volumes per cent is said to cause respiratory failure (Adriani, 1952*c*). Its potency, however, may be even greater than these estimates indicate; for they were probably based on the brief administrations for which the anaesthetic has always been exclusively used. Its solubility, however, is such that, during brief administrations, its tension in the brain would not reach half the inspired tension. Its true potency, therefore, may be at least twice as great as the above values suggest. It would not be surprising, in fact, if a concentration as low as 2 volumes per cent constituted an overdose if the administration was indefinitely prolonged.

As well as being very potent, ethyl chloride is extremely volatile; at room temperature it is a gas. Therefore, when the anaesthetic is sprayed on a mask, which is the usual method of administration, it might be given at any vapour strength up to 100 volumes per cent. An alternative way of giving it is to introduce 2 to 6 ml. of the liquid into a rubber bag and then allow the patient to breathe in and out [illegible]

this capacity, the initial vapour strength of the anaesthetic may often be well over 50 volumes per cent when it is given this way. Therefore, by either method of administration, the anaesthetic might easily be given at, say, thirty or more times a therapeutic concentration.

Finally, as a result of its low blood-solubility, its tension in the brain and heart would quickly reach, though less than half, at least a considerable fraction of its inspired tension.

measure that with any anaesthetic at once gives a high degree of protection against the dangers of respiratory complications. It is, however, the potentially much more dangerous circulatory complications that appear at present to form the main hazard with this anaesthetic. For even in normal clinical dosage, it has marked cardiovascular effects, which have not yet been fully explained. Raventós (1956) attributes the fall in blood pressure that so commonly occurs to a ganglion-blocking action; but the Medical Research Council's Committee on Non-explosive Anaesthetics (1957) were led by their experiments to regard the fall as more complex in origin. At least three mechanisms, they think, contribute to it, including a direct action on the heart, depressing its activity to an extent comparable with that seen in chloroform anaesthesia. Halothane, they state, looks disturbingly similar to chloroform in many respects, though they believe that, when its administration is properly managed, the danger of primary cardiac syncope during induction with it might be much less than with chloroform.

Speed of induction and recovery with halothane was at first thought to be very rapid and the incidence of post-anaesthetic vomiting gratifyingly low. But in neither of these respects was the Medical Research Council's Committee particularly impressed. The incidence of vomiting, they found, was little if any less than with other agents; and the speed of recovery was only moderately fast. The latter finding is entirely consistent with what one would expect from the anaesthetic's blood-solubility.

On certain points there appears to be general agreement: effective atropinisation of the patient prior to the administration of halothane is essential in order to prevent vagal inhibition of the heart, which is believed to be a danger with the anaesthetic; the pulse and blood pressure should be constantly watched so that the anaesthetic can be withdrawn or its concentration decreased the moment any adverse circulatory effect appears; the vapour strength should be strictly controlled and limited to three volumes per cent or even less (Brennan, 1957; Brennan *et al.*, 1957); and finally, the tendency of the anaesthetic to induce hypotension might constitute a special danger if the patient was anaesthetised upright, which may contra-indicate its use for patients in the dental chair.

The potency of halothane is probably greater even than that of ethyl chloride, and although the anaesthetic is less volatile and more soluble than ethyl chloride, it needs special apparatus to regulate its vapour strength if a dangerous overdose is to be avoided. Such apparatus has been devised and is available. Nevertheless, in the present state of knowledge, it would seem advisable to accept the recommendations of the Medical Research Council's Committee

simple apparatus consisting of a face-mask and a small breathing bag, between which is a vaporising chamber. In the chamber is placed 3 ml. to 5 ml. of the liquid anaesthetic. The mask is then applied and the patient breathes through the vaporising chamber in and out of the bag. After about a minute, anaesthesia is established and the administration is stopped. Anaesthesia then continues for about a further minute.

With this method, the danger of overdose is small or absent, since the total amount of anaesthetic is limited. However, the method is suitable only for young children. For older children and adults, the dose is insufficient and the method unsatisfactory, although it could probably be made satisfactory by using a larger bag and greater quantity of anaesthetic. Nevertheless, the method appears to me to be faulty in two respects·

1. *At the moment the mask is applied, the bag is empty.* An inspiratory valve allows the patient to take a breath of air which is then exhaled into the bag. The patient then breathes this sample of air throughout the administration, fresh air being drawn into the apparatus only in small amounts as breathing deepens. Not surprisingly, therefore, the oxygen concentration falls during the administration and the patient is often cyanosed when the mask is removed. To avoid this, some anaesthetists fill the bag with oxygen at the start. But divinyl ether is ignitable in air and forms explosive mixtures with oxygen. For reasons to be explained later, the explosion risk with ignitable anaesthetics and high concentrations of oxygen (or nitrous oxide) is one that should not be accepted in dental anaesthesia and therefore this practice is not recommended.

2. The duration and depth of anaesthesia are not uniform; sometimes they are insufficient for dental extraction, the operation for which the anaesthetic is most commonly used. This is presumably due to variations in vapour strength, some anaesthetic perhaps being lost while being transferred to the vaporising chamber from the glass ampoule in which it is dispensed. Although the total amount of anaesthetic is limited, the method is not dosimetric; it is empirical, and the anaesthetist has no knowledge of the vapour strength he is giving.

In spite of these drawbacks, however, the method appears to give fairly satisfactory results in small children and undoubtedly has a wide margin of safety. It should perhaps be used more extensively than it is at present

Halothane

The main advantage of this newly discovered anaesthetic is that it is non-ignitable and can therefore be used safely with oxygen, a

until 1941, after it had been investigated as a possible safe substitute for chloroform in war surgery.

Trichloroethylene shares with chloroform and halothane the advantage of being non-ignitable in oxygen or nitrous oxide under any conditions met with in surgical practice. Probably most anaesthetists regard it as a weak anaesthetic, scarcely in fact an anaesthetic at all when given alone, and *it is used almost exclusively for two* purposes: as an adjuvant to nitrous oxide in both ambulatory and non-ambulatory patients; and as an analgesic for patients in labour.

The view that trichloroethylene is a weak anaesthetic is entirely incorrect. It may even be the most powerful of all the inhalational anaesthetics. The mistake comes from failure to take into account its low volatilty and high blood-solubility.

Trichloroethylene boils at 87°C. This means that, by the open mask method of administration, the highest concentration that can *theoretically accumulate under the mask is about 6 volumes per cent*, and in actual clinical practice the amounts given are far less than this (Macintosh *et al.*, 1958*a*). Ordinarily, it is administered from the vaporising bottle of a nitrous oxide-oxygen anaesthesia machine. Given in this way and with the controls set in the position in which they are usually placed for continuous administrations, the anaesthetic is delivered at a vpour strength less than 0·5 volumes per cent (Mapleson, 1957). Yet, when this amount is administered with nitrous oxide and oxygen for a prolonged period and both anaesthetics are then withdrawn, anaesthesia continues for many minutes after the nitrous oxide has been eliminated. This suggests that concentrations less than 0·5 volumes per cent would be capable by themselves of inducing anaesthesia if the administration was sufficiently prolonged. The anaesthetic is therefore unquestionably of very high potency. Clinically it appears to be weak because its low volatility and high solubility prevent any but very low tissue tensions developing during administrations of ordinary length.

These physical properties make the anaesthetic safe: during short administrations, it is virtually impossible to give an overdose. It can therefore be handled by the 'occasional' anaesthetist and is safe for self-administration by the woman in labour. Unfortunately, however, these same physical properties limit the value of the anaesthetic in short administrations, as at once became apparent when it was tried as a sole anaesthetic for extraction of teeth in children. Induction was found to be very slow; and unless the amount given was kept down to the absolute minimum (whimpering during the extractions was regarded as the 'hallmark of success'), recovery was delayed, even as long as half an hour (Galley, 1945). The same disadvantage arises when it is used as *an adjuvant to nitrous oxide*. And likewise

that halothane should be administered only by trained anaesthetists Therefore, halothane, with such advantages as it may offer in ambulatory work (which appear to me to be limited by its not very low blood-solubility), cannot at present be widely used in this field.

Chloroform

Chloroform is more potent than halothane. Goodman and Gilman (1955*d*) give 0 2 to 1·5 volumes per cent as the range needed for surgical anaesthesia and state that breathing 2 volumes per cent for an extended period proves fatal.

With this very soluble anaesthetic, induction and recovery are slow; and prolonged inhalation is needed to obtain the maximum effect of any given concentration. This has long been known, although the reason for it was not understood. In *Hewitt's Anaesthetics and Their Administration* (Robinson 1922*b*) it was stated that a concentration that induces anaesthesia only after thirty minutes will, after two hours, produce respiratory arrest.

It has always been standard practice with chloroform to accelerate induction by giving the anaesthetic at concentrations that are in fact many times a lethal dose, its volatility allows this. The danger is that, with the open mask method of administration, the one usually used, the anaesthetist has no way of knowing even approximately the vapour strength he is giving. An overdose is therefore all too readily given. This is the danger to which Snow constantly called attention. Throughout his life, Snow insisted on the need for accurate control and limitation of its vapour strength, and in 1858, the year of his death, he was able to report that he had given chloroform to more than 4,000 patients with but a single death, and that not attributable to the anaesthetic—a record that would have been remarkable with any anaesthetic in those pioneering days.

Perhaps if chloroform were used today with the same careful measurement and limitation of dose that is the practice with halothane, it would prove no more dangerous in its immediate effects and might, on account of its higher blood-solubility, be even less dangerous than halothane. Accurate and fool-proof apparatus for using it in this way has been devised. Nevertheless, even if, with such apparatus, it could be safely handled by 'occasional' anaesthetists, its high blood-solubility would not allow the rapid recovery needed in ambulatory patients. For this reason alone it would be unsuitable for this work.

Trichloroethylene

Trichloroethylene was introduced as an anaesthetic in America in 1935; but it did not begin to be widely used in the United Kingdom

until 1941, after it had been investigated as a possible safe substitute for chloroform in war surgery.

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in midwifery, little relief from the pains of the first stage of labour is gained for some time; and later, when intermittent administration has been in progress for several hours, cumulative effects result and patients are apt to become stuporous and uncontrollable.

This slowness of action is the direct outcome of the anaesthetic's high blood-solubility. I have stressed the necessity for anaesthetics of low blood-solubility in work with ambulatory patients. In midwifery also, where the need is for pain-relief of rapid onset and short duration repeated every few minutes for an indefinite period, the choice should lie with agents of low blood-solubility. Trichloroethylene is too soluble for these purposes.

Ether

The slowness of induction and recovery with ether, the most soluble of all the inhalational anaesthetics, makes it totally unsuitable for our purpose.

Conclusions

Of the eight anaesthetics reviewed above, it may be said broadly that nitrous oxide and ethylene are too weak, ethyl chloride too dangerous, and chloroform, trichloroethylene and ether too soluble to meet the requirements of anaesthesia in ambulatory patients Only divinyl ether and possibly halothane (if further trial excludes cardiac syncope as a possible danger with this anaesthetic) come near to doing so. There remains to be considered cyclopropane, the most interesting anaesthetic of all from the point of view of the present discussion.

Chapter IX

CYCLOPROPANE

In reporting their discovery of the anaesthetic properties of cyclopropane, Lucas and Henderson (1929) referred to the gas as "a remarkably potent anaesthetic". This estimate of its potency was reaffirmed in the first clinical reports: "cyclopropane is very powerful and rapid in its action" (Stiles *et al.*, 1934); it is "of the potency of chloroform or ether, but without their irritant qualities" (Waters and Schmidt, 1934). Lack of irritant qualities was regarded as a danger, since it meant that high concentrations could be inhaled without producing laryngeal spasm and the patient might therefore be given an overdose. Subsequent clinical reports all stressed the potency of the anaesthetic: it was capable of inducing deep anaesthesia very rapidly in any patient; respiration could easily become arrested even in the presence of a plentiful supply of oxygen; "Respect the potency of cyclopropane", Griffith (1953) gave as the first rule for its safe use. Thus the notion that cyclopropane was extremely potent became established doctrine, and the natural corollary was that it was safe only in experienced hands.

This virtually ruled it out as an anaesthetic for ambulatory patients. Moreover, the alleged ease with which patients could be overdosed was not the only threat to deter less experienced anaesthetists. Cardiac arrhythmias had been noticed; and these included, though perhaps rather rarely, multi-focal ventricular tachycardia, generally regarded as a precursor of ventricular fibrillation. Sudden heart failure, therefore, appeared to be a possibility, and many experienced anaesthetists became hesitant about using the anaesthetic.

In addition, there was the risk of explosion. Cyclopropane is ignitable in air, and mixed with oxygen in the proportions ordinarily used in clinical practice, it is explosive. As with ether and ethylene, on rare occasions an explosion occurred.

Altogether there seemed ample justification for regarding cyclopropane as an anaesthetic that should be handled only by trained anaesthetists fully conversant with its dangers. It seemed totally unsuitable for use by those with limited experience. Moreover, its supposed high potency appeared, in the light of accepted precepts, to ally it to major not minor surgery.

These opinions, reasonable enough at first sight, became and have remained so deeply rooted that cyclopropane has never been extensively tried in ambulatory work. They are, however, fallacious, and in fact, as I shall try to show, cyclopropane, both in theory and in practice, meets the requirements of ambulatory work more nearly than any other anaesthetic. Let us consider first the question of its potency.

Potency of Cyclopropane.—Waters and Schmidt (1934) and Seevers *et al.* (1937) appear to be the only workers who have attempted to relate the amounts of cyclopropane in inspired air to the depth of anaesthesia they produce in man.

Waters and Schmidt's method was to measure the content of cyclopropane in gas samples drawn from beneath the face mask when no change had been made in the mixture delivered from the anaesthesia machine for at least five minutes. Simultaneously they observed the level of anaesthesia. Their average findings in 46 patients were as follows:

Concentration of Cyclopropane	*Level of Anaesthesia*
7·4%	Light surgical anaesthesia (Stage III, Plane 1)
13·1%	Medium surgical anaesthesia (Stage III, Plane 2)
23·3%	Deep surgical anaesthesia (Stage III, Plane 3)
42·9%	Respiratory arrest (Stage IV)

(Concentrations causing respiratory arrest, they noted, were not harmful provided that artificial respiration was effectively maintained.)

These results suggest that cyclopropane has more than ten times the potency of nitrous oxide; for the tests reported in Chapter VII showed that light surgical anaesthesia was barely reached with 80 per cent nitrous oxide. The method, however, does not provide a basis for exact comparison, since five minutes is not long enough to get the full effect of any given concentration of cyclopropane. With longer administrations, the same levels might have been reached with smaller amounts. Therefore, although the results are the average findings in 46 patients, in some of whom the time interval may have been a good deal longer than five minutes, the percentages given may be too high. This consideration, however, is to some extent offset by the fact that the patients had been given morphine as pre-anaesthetic medication. Without morphine, more cyclopropane might have been needed.

The method of Seevers and his colleagues allows a more precise

comparison of the two anaesthetics. They studied the concentrations of cyclopropane and nitrous oxide needed to produce equal degrees of analgesia. They also observed the amounts needed for loss of consciousness. No pre-anaesthetic medication was given, and the same subjects (volunteers, not patients) were used for all experiments. Furthermore, they compared the effects of the two anaesthetics after administrations of equal length (five minutes and ten minutes). This was fortunate, for the blood-solubilities of cyclopropane and nitrous oxide are virtually equal and therefore after administrations of equal length the brain would have reached the same degree of saturation with the two anaesthetics.

Their findings consistently suggest that cyclopropane has about eight times the potency of nitrous oxide. The results they obtained with administrations of ten minutes duration may be stated as follows:

	Cyclopropane (per cent)	*Nitrous oxide (per cent)*
Onset of analgesia	2·5	20
Analgesia of specified degree	4	35
Loss of co-operation	5	40
Loss of consciousness	6	35–45

This places cyclopropane in a unique position amongst the available anaesthetics: it is a good deal more powerful than nitrous oxide, but compared with the other anaesthetics it is weak. Divinyl ether has more than twice its strength, ethyl chloride and ether about five times its strength, and halothane, chloroform and trichloroethylene at least ten times its strength. Far from being extremely powerful it is in fact the second weakest anaesthetic. It stands alone in the wide gap that separates nitrous oxide from the others. Its potency is intermediate.

Anaesthetists seem to have overlooked this evidence and to have been misled by clinical appearances. Cyclopropane, they noted, unlike the other anaesthetic gases, was capable of inducing all levels of anaesthesia, including respiratory arrest. Anaesthetics with this potentiality were customarily classed together as 'a hundred per cent potent'. But its most striking property was its speed of action; and although this was due mainly to the anaesthetic's low blood-solubility, it was mistaken, understandably perhaps, for evidence of extreme potency.

In ambulatory work, an anaesthetic of intermediate potency and very low blood-solubility is precisely what is needed. Cyclopropane is the least soluble of all the available inhalational anaesthetics. Consequently, its speed of uptake and elimination is greater than that of any other. Since its blood-solubility is almost identical with

that of nitrous oxide, the rates at which its tension in arterial blood and in the brain approach equilibrium with a constant inspired concentration can be followed in Fig. 7 (p. 46). If cyclopropane were given at an inspired concentration of ten volumes per cent, which is roughly equipotent with nitrous oxide at 80 volumes per cent, the same effects might be expected as were reported for nitrous oxide in Chapter VII: induction would take ten minutes, and anaesthesia would often be too shallow. Now depth of anaesthesia, as I have stated, is not sensitive to small increments of anaesthetic. With nitrous oxide, the inspired concentration could be increased only to the extent of 25 per cent of the amount to which I have just referred, and then only by the total exclusion of oxygen. Even if this increase could be maintained, it would add but little to the depth of anaesthesia. With cyclopropane, the concentration that is equipotent with 80 per cent nitrous oxide could be increased up to eightfold without reducing the oxygen below physiological levels. The higher potency of cyclopropane, therefore, gives it scope to provide a satisfactory depth of anaesthesia very rapidly in any patient. But there now enters the possibility of overdose.

The danger of overdose with cyclopropane has been exaggerated. The margin of safety between its anaesthetic and its lethal concentrations is considered by Goodman and Gilman (1955*g*) to be, perhaps, wider than with any other anaesthetic; and indeed this is only to be expected from its relatively low potency. Its anaesthetic range runs up to concentrations higher than 30 volumes per cent (Seevers and Waters, 1938), so that at worst it could be given at only three times a therapeutic amount. This is in sharp contrast with ethyl chloride, for example, the potency of which, as explained above, is such that it might be given at thirty or more times a therapeutic amount. As a result of its relatively low potency, even very high concentrations of cyclopropane would not constitute a gross overdose. And the danger of arresting respiration could easily be avoided by keeping the concentration within certain *limits*.

Experience with cyclopropane in routine in-patient work indicates where these limits should be set. When cyclopropane, unsupported by any other central nervous system depressant, is given at a constant inspired concentration of 50 volumes per cent (with 50 per cent oxygen), consciousness is lost in three to six breaths; anaesthesia is established within a minute; after about three minutes, the laryngeal reflexes are abolished and anaesthesia is deep enough for tracheal intubation; and after four or five minutes respiration, which has been *steadily decreasing in amplitude, gradually ceases*. These facts may be verified in everyday practice, although the maxi-

mum flowrate of cyclopropane delivered by standard apparatus* is not sufficient to provide for a constant inspired concentration of 50 volumes per cent except in infants and small children. In such patients, I have used this method of induction routinely for several years for the purpose of establishing endotracheal anaesthesia. The results are remarkably uniform. The point at which anaesthesia is established is marked by the usual signs and is easily identified. The progress towards deeper levels of anaesthesia is gradual; there is never any danger of sudden respiratory arrest. Even an inexperienced anaesthetist could not fail to notice the trend and recognise in good time the need to reduce the concentration or withdraw the anaesthetic; and even when this is intentionally delayed almost to the point of respiratory arrest, respiration quickly recovers spontaneously. The rate at which respiration fails with this concentration of cyclopropane compares very favourably with that seen sometimes with ethyl chloride given in overdose, or with nitrous oxide if oxygen restriction is carried a little too far, when respiration may cease suddenly and without warning, and may not easily be restarted. It seems, therefore, that a concentration of 50 volumes per cent would be safe for brief administrations, and that if steps were taken to guard against this amount being exceeded, the anaesthetic could be used without danger of overdose by anaesthetists of limited experience. A simple and foolproof method of using cyclopropane that starts with this concentration and ensures an automatic reduction of strength as the administration proceeds will be described in Chapter X. With this method, cyclopropane need no longer be regarded as too powerful for use by the 'occasional' anaesthetist.

Cardiac Effects of Cyclopropane.—However suitable an anaesthetic might be in other respects, it could not be used in ambulatory work if there was risk of its causing cardiac syncope. The question whether the cardiac effects of cyclopropane are dangerous or not is therefore of prime importance.

There is no evidence to suggest that cyclopropane is toxic to the myocardium, like chloroform and perhaps the other halogenated anaesthetics. Blood pressure is well maintained even when cyclopropane is given in amounts that arrest respiration, provided that artificial respiration is effectively carried out. The point at issue is the effect of the anaesthetic on cardiac rhythm; and the vital question is can cyclopropane precipitate ventricular fibrillation?

* A Boyle's machine with a [illegible] up to 1 6 L/min. [illegible] of the cycloprop[illegible] sufficient to prevent rebreathing, which dilutes the mixture with air from the lungs, interferes with lung washout and delays induction. Cyclopropane flowmeters should be calibrated in gradations of one litre up to 5 L/min.

A great deal of animal experimentation has been undertaken in an attempt to elucidate this problem. Disorders of rhythm are a common clinical occurrence with every anaesthetic (Seevers and Waters, 1938). With cyclopropane they tend to have a ventricular origin, and in this cyclopropane resembles chloroform. Most of the experimental work with cyclopropane has therefore followed the lines of the well-known study of chloroform made by Levy nearly 50 years ago. Levy found that chloroform increased the sensitivity of the cat's heart to adrenaline: under light chloroform anaesthesia, the cat more readily developed ventricular fibrillation in response to injected adrenaline than it did in the absence of chloroform. Ventricular fibrillation was preceded in the cat by multifocal ventricular tachycardia; and since this disorder of rhythm had been observed with chloroform in man, Levy suggested that the occasional death that occurred with this anaesthetic during the excitement stage of induction might be due to ventricular fibrillation precipitated by endogenous adrenaline.

This explanation was widely accepted and is current today. In the study of cyclopropane, therefore, attention has been directed mainly to its action in increasing the heart's sensitivity to adrenaline and related compounds.

This and other work on the cardiac effects of cyclopropane in animals and man has been reviewed by Seevers and Waters (1938), Meek (1941), Dripps (1947), Dawes (1952), Goodman and Gilman (1955*h*), Robbins (1958) and others. The following facts appear to have been established.

1. As a direct cardiac depressant, cyclopropane is less active than either chloroform or ether. With effective artificial respiration, blood pressure does not begin to decline until the concentration of cyclopropane reaches 50 per cent to 60 per cent: respiration always stops before the circulation begins to fail.

2. Cyclopropane by itself, that is to say, without adrenaline, gives rise to arrhythmias both in man and in the dog. The arrhythmias usually begin to appear as respiratory arrest is approached (about 40 per cent cyclopropane) and increase in incidence and severity as the concentration of cyclopropane is raised. With effective artificial respiration, their onset may be delayed in the dog until much higher concentrations, even as high as 72 per cent, are reached. Hypoxia of cardiac muscle greatly favours their occurrence; it is a strongly predisposing factor, and in one dog whose respiration became obstructed, arrhythmias occurred with cyclopropane at a concentration of only 18 per cent.

3. Adrenaline and related compounds by themselves, that is to say, without cyclopropane, are capable of precipitating in the dog

and other mammals arrhythmias of various kinds, including ventricular tachycardia and fibrillation.

4. In the dog, this sensitivity to adrenaline is much increased by cyclopropane, only slightly by chloroform and not at all by ether. In light cyclopropane anaesthesia, the increase is slight; it becomes pronounced only in deep anaesthesia, when as little as twice the amount of adrenaline that might be secreted by the animal may be sufficient to give rise to ventricular tachycardia or fibrillation. However, if the administration of cyclopropane is prolonged, susceptibility to adrenaline-precipitated ventricular fibrillation becomes reduced or is lost.

5. In the cat, sensitivity to adrenaline is increased only slightly if at all by cyclopropane, but to a very marked extent by chloroform, particularly in light anaesthesia. Sensitivity becomes less as chloroform anaesthesia deepens, and finally it disappears: deep chloroform anaesthesia actually protects the cat against adrenaline-induced arrhythmias.

6. Cyclopropane in combination with moderate amounts of adrenaline may give rise to ventricular fibrillation in the dog, but not in the cat, guinea-pig, rat or rabbit; chloroform with moderate amounts of adrenaline may have this action in the dog, cat and guinea-pig, but not in the rat or rabbit (Hutcheon, 1951)

7. Though cyclopropane and chloroform increase the sensitivity of the myocardium to adrenaline in certain animals, there is no convincing evidence that they increase excitability, rhythmicity or conduction velocity; on the contrary, they are depressants in every sense (Dawes, 1952)'

8. Cyclopropane increases heart rate in the dog, but decreases it in man.

When these facts are reviewed, it seems doubtful whether the results of animal experiments give any guide as to what might happen with cyclopropane in man. Clearly, there are wide species-differences. And if we accept Levy's explanation of chloroform deaths, it does not follow that the same danger will arise with cyclopropane; for the difference between the two anaesthetics in relation to their production of arrhythmias is wide—so wide, in fact, that Dawes questions whether they really produce arrhythmias in precisely the same way Dawes was unable from his study to form any opinion on the fundamental nature and mechanism of cardiac arrhythmias in man. His ultimate purpose was the assay of quinidine-like drugs, and he concluded that we were bound to proceed for some time to come on an empirical basis.

In my view, whether cyclopropane can precipitate ventricular fibrillation in man is a question, also, that can be answered as yet

only on an empirical basis. Fortunately, cyclopropane has now been widely used for a quarter of a century. From time to time large series of administrations have been reported. It is mainly on these reports that we must rely for evidence of its safety or danger. But first we may consider the evidence from its use in the rather special circumstances of cardiac surgery. Here, the number of cases is relatively small, but the situation is particularly advantageous for detecting any adverse cardiac effect of an anaesthetic: first, the heart is exposed during most of the operation, so that the occurrence of arrhythmias, asystole or ventricular fibrillation can be directly observed; and second, in many instances the myocardium is hypoxic. Hypoxia greatly favours ventricular fibrillation; the ventricle becomes so sensitive that pricking it with a needle, or even touching it only, may precipitate fibrillation (Milstein and Brock, 1954). Therefore, it seems reasonable to suppose that if cyclopropane were specially prone to cause fibrillation, it would do so in these cases and the fact would soon become apparent.

The evidence from this field does not point to such a tendency. Milstein and Brock (1954) made a study of ventricular fibrillation during cardiac surgery based on its occurrence in 30 out of many hundreds of patients operated on. They found that analysis of the anaesthetic in the 30 cases did not reveal any common factor: ventricular fibrillation was no more likely to occur with cyclopropane than it was with the other anaesthetics they used, which included thiopentone, ether and nitrous oxide. Cyclopropane was selected as the anaesthetic of choice for the most severe cases and all those that were cyanosed. In a few cases ventricular fibrillation occurred, as it did with the other anaesthetics; but in several hundred cases, cyclopropane had no untoward effect. It is, however, only fair to point out that cyclopropane was withdrawn if multiple ventricular extrasystoles occurred. Nevertheless, these authors considered that, of the many drugs used in cardiac surgery, including the anaesthetics, the only one of importance in the production of ventricular fibrillation was adrenaline.

Ziegler (1948) reported 175 consecutive cases in which the Blalock-Taussig operation was performed in children for congenital heart disease with cyanosis. The anaesthetic used was cyclopropane to which small amounts of ether were added after induction. He made the interesting observation that in not a single case did ventricular fibrillation occur, even though adrenaline was sometimes administered in large amounts.

Cooley (1950) found that the administration of adrenaline with cyclopropane not merely failed to precipitate ventricular fibrillation: it did not give rise to any form of arrhythmia. This may have been

due to the fact that procaine was administered with the adrenaline; but it now seems doubtful whether procaine confers protection. Cooley's report was based on 878 operations for pulmonary stenosis performed by Blalock at the Johns Hopkins Hospital. In 48 cases the heart became arrested, but in none did ventricular fibrillation occur. The anaesthetic used is not directly stated, but it may be inferred that in most if not all cases it was cyclopropane. Milstein and Brock, Ziegler, and Cooley, independently suggest that the main cause of asystole or ventricular fibrillation is myocardial hypoxia.

Turner (1959) considers that retention of carbon dioxide is also an important cause. He is firmly of the opinion that serious arrhythmias do not arise with cyclopropane when ventilation of the lungs is properly maintained. His views are based on more than 750 heart operations performed under cyclopropane anaesthesia in Edinburgh. Extrasystoles, he states, may occur with cyclopropane and give the electrocardiograph tracings an alarming appearance, but they are, in fact, entirely benign. He believes the incidence of ventricular fibrillation in heart operations to be lower with cyclopropane than with other anaesthetics.

It seems reasonable to suppose that if ventricular fibrillation was in fact a danger with cyclopropane, the use of this anaesthetic would have been abandoned in cardiac surgery. Cyclopropane has long been suspect as a possible cause of this disorder, and its tendency to produce arrhythmias is well known. Yet far from being abandoned, it has come to be regarded in many clinics as the anaesthetic of choice in cardiac surgery. We may now consider evidence from the broad field of general surgery.

Waters and Gillespie (1944) made a study of the deaths that occurred in the operating theatres of the Wisconsin General Hospital during the ten year period, 1933 to 1942 inclusive. During this period, which covers the first ten years of the clinical life of cyclopropane, about 40,000 patients received general anaesthesia of one kind or another, including intravenous; in 22,000 of them the anaesthetic was cyclopropane. In the whole group of 40,000 patients, there were 25 fatalities in which death was due wholly or in part to anaesthesia. Seven of them occurred with cyclopropane. Waters and Gillespie considered that in at least two of the seven, maladministration and not the anaesthetic was at fault. In the remaining five, the circumstances, they thought, were suggestive of abrupt cardiac failure; and in two of these they had no doubt that primary cardiac failure was the cause of death. Fortunately, Waters and Gillespie gave detailed descriptions in their report of all seven cases. When these cases are reviewed today, considerable doubt may be felt as

to whether every one of them could not be better explained on the basis of maladministration. It is worth noting that of the two cases in which Waters and Gillespie thought the anaesthetic itself was undoubtedly to blame, in one, death followed partial obstruction of respiration, and in the other, that of a woman of 55, weighing 14½ stone (203 pounds or 92 Kilos) and only 5 ft. 1 in. (1·55 metres) in height (the sort of case that might very well give rise to difficulties), carbon dioxide was allowed to accumulate and respiration became depressed and almost arrested. At autopsy in this case, the heart was found to be fibrotic and arteriosclerotic. It is worth noting also that with ether, which was used in about 10,000 cases in this series and which is generally held to be a very safe anaesthetic, there were five fatalities in which death was due wholly or in part to anaesthesia. Thus the death rate with ether was higher than it was with cyclopropane. Waters and Gillespie concluded that in their hands *cyclopropane was no more dangerous than other anaesthetics.*

A study of cyclopropane reported by Guedel (1940) and covering the first eight years of its clinical life is of special interest. During this period, Guedel and his associates used cyclopropane in more than 8,000 patients. During the first six years of the study, they were aware of the occurrence of arrhythmias but paid little attention to them. After this, however, the fear of arrhythmias with cyclopropane that current teaching had built up persuaded them to study the arrhythmias more closely.

They found that arrhythmias appeared about at the point of apnoea They observed all types, including ventricular tachycardia, sometimes with heart rates of more than 200 When this occurred, instead of withdrawing cyclopropane or at least decreasing its concentration, which was the usual practice, they gave more cyclopropane and found that in most cases the heart returned to a normal rate and rhythm They believed there was an arrhythmic range, running from 20 to 30 per cent up to 40 to 70 per cent cyclopropane. Using artificial respiration and ignoring any arrhythmias that occurred, they frequently gave the anaesthetic for long periods at a concentration of 75 per cent in order to attain their objective, which was to provide abdominal relaxation as perfect as that given by spinal anaesthesia. It is difficult to imagine a more rigorous test of an anaesthetic's safety.

On completion of this study, Guedel concluded that arrhythmias occurring during cyclopropane anaesthesia need not be feared.

Griffith (1951) reported 20,000 administrations of cyclopropane that he himself had conducted with but a single death, which he did not attribute to the anaesthetic. The patients were unselected and included "all kinds of poor risk cases", many of whom had heart

disease of one kind or another and were in heart failure. His experience led him to think that cyclopropane was the anaesthetic of choice for "bad risk cases" and for patients with serious heart disease who had to undergo a major operation.

Another large series was reported by Samson (1956). He used cyclopropane without a single fatality in about 10,000 patients of all ages, many of whom had serious heart disease.

Such records as these are indeed remarkable and perhaps unequalled with any other anaesthetic in in-patient work. Recent figures from a group of ten teaching hospitals in the United States of America give an overall mortality from anaesthesia, all methods included, of 1 in 2,680 cases, where anaesthesia was directly and solely responsible for the fatality; and when cases are included in which anaesthesia was not solely responsible but played an important part, the mortality is as high as 1 in 1,560 cases (Beecher and Todd, 1954). This American study of deaths associated with anaesthesia and operation, a prospective inquiry into every death that occurred in about 600,000 patients admitted to the departments of surgery in the hospitals concerned during a five year period, is the most extensive ever made. Unfortunately, the report is in the form of a statistical analysis. Case histories are not given; and no mention is made of ventricular fibrillation with cyclopropane, which was used in about 50,000 of the patients. Therefore, from the point of view of the present discussion, the study is of no assistance.

One further piece of evidence, based on case histories, remains to be considered. In 1949, the Association of Anaesthetists of Great Britain and Ireland began an inquiry into the cause of deaths associated with anaesthesia in the United Kingdom. Anaesthetists were invited to report, with all relevant data, any death that occurred, and a committee was formed to study and analyse the reports. After about five years, 1,000 reports had been received and the committee published their findings (Edwards *et al.*, 1956). An unpublished finding, kindly communicated to me by Morton, a member of the committee who examined the reports, was that in not a single case did the data suggest that death had been due to ventricular fibrillation during anaesthesia with cyclopropane. There was no example of sudden and unexplained cardiac arrest with this anaesthetic. The published report, however, referred to nine cases in which trichloroethylene appeared to have precipitated 'primary cardiac failure'. It is possible to compute roughly from figures published by the Chief Medical Officer of the Ministry of Health (1955) that, over the period during which the 1,000 reports were received, cyclopropane had been used in about one million and trichloroethylene in about three million administrations of anaesthesia in hospital practice in England

and Wales. (There are no figures for Scotland and Northern Ireland) From this it seems that death from sudden heart failure is more exceptional with cyclopropane than it is with trichloroethylene. It cannot be said that no case occurred in this large number of administrations of cyclopropane, since reporting was voluntary, and there was good evidence, as the committee pointed out, that not all deaths were reported. But it seems reasonable to conclude from this evidence that death from sudden heart failure with cyclopropane, if it occurs at all, is exceedingly rare.

I do not wish to suggest that the question of ventricular fibrillation with cyclopropane is finally settled by the evidence I have given. But the evidence seems to show that the risk of meeting with this accident is not of sufficient magnitude to contra-indicate the use of cyclopropane in ambulatory work.

The Explosion Hazard with Cyclopropane.—The third contra-indication to the use of cyclopropane by the 'occasional' anaesthetist was its ignitability—the explosion hazard This will be discussed in Chapter X in connection with the proposed method of using the anaesthetic. It is sufficient to state here that the method entails the use of mixtures with which the explosion hazard is eliminated.

Thus the three main objections to the use of cyclopropane by the 'occasional' anaesthetist—the danger of overdose, the risk of cardiac syncope and the hazard of explosion—are either invalid or can be overcome. And, in fact, far from being contra-indicated, cyclopropane, with its intermediate potency, its very low blood-solubility and its freedom from toxicity, seems more suitable than any other anaesthetic for work with ambulatory patients. Extensive clinical trial of cyclopropane in this field appears to be fully justified.

Chapter X

CLINICAL TRIAL OF CYCLOPROPANE

REPORTS on the use of cyclopropane in ambulatory patients are few. The earliest was a brief communication by Amiot and Lattès (1939) to the *Société de Stomatologie de Paris* shortly before the outbreak of war. Using it for dental extraction, they gave the anaesthetic at concentrations of 25 per cent or 33 per cent with oxygen from a face mask. The administration was stopped after one half to three minutes, giving anaesthesia lasting up to four minutes after removal of the mask. Induction and recovery were rapid, and they found the anaesthetic in every way superior to nitrous oxide, but thought it should be used only by "competent" anaesthetists.

No further report was made until 1944, when dental anaesthesia was discussed at The Royal Society of Medicine and Pinson (1945) described the use of cyclopropane in 500 children under the age of 12; a quarter of the administrations were by students. He used low concentrations, and both induction and recovery were slower than with nitrous oxide. Disadvantages he found were salivation, and, during recovery, vomiting, which occurred in 21 per cent of cases. This led him to reserve the anaesthetic for the minority of patients, in whom there was a special indication; for routine work he preferred standard methods. He concluded that his method was safe, but it was somewhat cumbrous and does not seem to have been widely tried.

In the same discussion Gillies (1945) spoke of the use of cyclopropane as a supplement to nitrous oxide in more than 800 ambulatory dental patients. He emphasised its value in allowing full oxygenation and "very adequate anaesthesia and muscular relaxation with consequent avoidance of 'smash and grab' surgery."

None of these authors suggested the general adoption of cyclopropane in place of nitrous oxide in work with ambulatory patients, and no further reports were made.

Cyclopropane in Preset Concentration.—My own experience with cyclopropane in ambulatory patients began in June, 1947, when I was asked to give nitrous oxide to a man aged 45 for the incision and drainage of a septic finger. He was large and muscular, formerly a commando, and accustomed to considerable amounts of alcohol. Arrangements had been made for him to come to a nursing home

for the operation at 9 o'clock in the morning (without pre-anaesthetic medication), and he was to be at work in his office an hour later.

At that time, the earlier reports that I have referred to were unknown to me; but I decided, as no doubt other anaesthetists would have done, to use cyclopropane. My method was simple: a six litre bag was filled with 50 per cent cyclopropane and 50 per cent oxygen; the patient then breathed in and out of the bag, carbon dioxide being absorbed in a soda-lime canister between the bag and face mask.

The result was satisfactory. Induction was rapid, and anaesthesia uneventful. There was no salivation or post-anaesthetic vomiting. Recovery was almost as rapid as with nitrous oxide, and the patient was at work within the hour.

It was my experience with this case that prompted me to study this field of anaesthesia. The simplicity, effectiveness and apparent safety of my method led me to consider whether it might not prove more satisfactory in the hands of the 'occasional' anaesthetist than the customary one with nitrous oxide, which I had long regarded as unsatisfactory. I therefore made further trials in ambulatory patients, simplifying the method in short cases by omitting the soda-lime canister, but in longer cases retaining the canister and replenishing the oxygen at a flowrate of 300 ml. per minute.

Four years later I described the method in a preliminary communication based on 150 cases and suggested that it might, with advantage, replace the time-honoured one with nitrous oxide (Bourne, 1951) The following year I reviewed 1,000 administrations, most of them to dental patients, and repeated my suggestion (Bourne, 1952). And in 1954 I reviewed nearly 2,000 administrations, and again repeated my suggestion (Bourne, 1954*a*).

Following this communication, an almost identical method began to be developed by Hingson (1954) in the United States. He used cyclopropane and oxygen in equal parts, as I had done; but at first he used a three-litre bag and in longer cases added oxygen at flowrates of 400 ml. to 600 ml per minute. Later he used a six-litre bag and other mixtures.

The Explosion Hazard.—The mixture I had been using was ignitable and probably explosive; but up to this point I considered that the risk of ignition was negligible. A spark from static electricity coming into contact with the mixture seemed to me impossible with the method; and so long as the anaesthetist took care to extinguish any nearby flame, I considered that ignition would not occur. There was, however, a source of ignition that appears till then to have been unthought of: sparks of the flint and steel variety may be thrown off

when a forceps slips from a tooth during extraction.* This fact became known when Newton-Andrews (1954), a general medical practitioner, reported that, while giving nitrous oxide to a patient, he had seen a shower of sparks, plainly visible in a well-lighted surgery.

This observation contra-indicated the use of my method for dental extraction, which is done immediately the anaesthetic is withdrawn, when the exhalations may be ignitable; and I suggested that the method should be abandoned in dentistry until the matter had been investigated (Bourne, 1954*b*).

Experiments by Morton and myself confirmed that sparks could be formed in this way (Bourne and Morton, 1955). We got sparks that sometimes flew a foot or more and were visible in bright daylight when dental forceps were made to slip and fracture the enamel of a tooth. We found that the ease with which the sparks could be obtained, and their number and brilliance, increased when the surrounding atmosphere was enriched with oxygen.

With these sparks we ignited in turn cyclopropane, ether and divinyl ether in oxygen. Experimenting further with cyclopropane, we found that ignition became increasingly difficult when the oxygen was diluted with nitrogen. When the concentration of oxygen reached as low as 30 per cent, we failed to ignite cyclopropane in a hundred consecutive attempts, at each of which good sparks were seen.

A grindstone applied to dental forceps threw off a stream of sparks far in excess of any that could be got from teeth. With these sparks we ignited cyclopropane with oxygen concentrations as low as 28 per cent, but failed to ignite it throughout its entire ignitable range with concentrations of oxygen that were 25 per cent or less.

From these experiments we concluded that ignition of cyclopropane by sparks from teeth and dental forceps was unlikely when the concentration of oxygen in the mouth did not exceed 30 per cent and was improbable in the extreme when the concentration was 25 per cent or less. We found that the oxygen concentration in the exhalations of patients anaesthetised from the six litre bag filled with 50 per cent cyclopropane and 50 per cent oxygen did not fall to 25 per cent until about five breaths of air had been taken, and we considered that during this interval the patient was at risk.

The solution of the problem was to use less oxygen. Thenceforward the bag was filled with 50 per cent cyclopropane, 25 per cent

* In the privately circulated *Newsletter of the Australian Society of Anaesthetists*, Kaye reported in 1954 that in 1946 a spark struck in this way ignited a nitrous oxide-oxygen-ether mixture and the patient's mouth was burned. This appears to be the only instance on record.

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as nitrogen). When the mixture is discharged from the bag, it becomes diluted with air and follows the line AB, crossing the ignitable range just above the 20 per cent oxygen line; but when a patient breathes in and out of the bag, the mixture is diluted, not with atmospheric air, but with air from the lungs, and dilution follows the line AC. If the administration were continued until the bag and lung contents were evenly mixed, dilution would reach a point roughly one third of the way along AC. If the administration were then stopped and the patient were left breathing air, the composition of his exhalations would closely follow the remainder of the line AC, passing through the ignitable range below the 20 per cent oxygen line—a fact that has been verified in patients anaesthetised with the method. (For analysis of their exhalations I am indebted to the Research and Development Department of the British Oxygen Company Limited. The results are given in their report No. E 2081).

The American Modification.—While our experiments with nitrogen

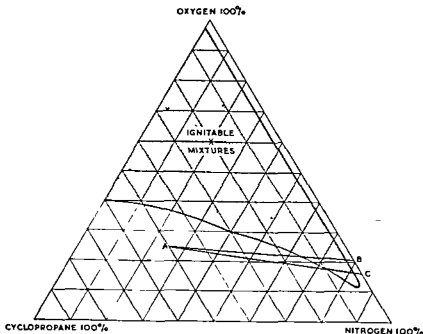


FIG 13 —Ternary combustion diagram* representing all possible mixtures of

* Constructed by The Research and Development Department of The British Oxygen Company Ltd. from data given by Jones, G W., Kennedy, R. E. and Thomas, G J. (1943). United States Bureau of Mines, Technical Paper 653, and Hass, H. B , Hibshman, H. J. and Romberger, F. T. (1940) *Anesthesiology*, 1, 31.

oxygen and 25 per cent nitrogen. With this mixture, with which anaesthesia was no less satisfactory, we found that patients' exhalations never contained more than 23 per cent oxygen. Thus the danger of ignition by sparks from teeth and dental forceps was overcome.

Elimination of the Explosion Hazard.—The use of 25 per cent instead of 50 per cent oxygen provided an additional safeguard: it made the mixture in the bag too rich in cyclopropane to be ignited by any source of ignition. However, if the mixture were discharged from the bag into a flame, the cyclopropane would catch fire, since on leaving the bag it would become diluted with air and enter its *ignitable range. Nevertheless, by the time the cyclopropane* had reached this range, the oxygen also would have become diluted and would have reached an amount only just above 20 per cent, at which level neither cyclopropane nor any of the ignitable anaesthetics can be made to explode; they simply catch fire and burn (Macintosh, *et al.*, 1958*b* and *c*). Thus the use of this mixture not merely abolished the risk of ignition by sparks from teeth and dental forceps: it eliminated any possibility of an explosion.

This fact was easily verified. When I discharged the bag into a flame, the cyclopropane caught fire; but there was no explosion and the flame did not travel back into the bag. And when I recharged the bag and held it over a flame until a hole was burned, the emerging gas caught fire and burned; but there was again no explosion and no fire within the bag.

With the exhalations of a patient anaesthetised with this mixture, the risk of ignition after withdrawing the anaesthetic would probably be very small. For expired air contains only 16·3 per cent oxygen. Therefore, when the cyclopropane in the exhalations had fallen to the range at which it could be ignited, the oxygen concentration would be less than 20 per cent and the mixture close to the ignitable limits. Mixtures near the ignitable limits are difficult to ignite. To ignite the exhalations, therefore, it would probably be necessary to have a strong source of ignition, such as a flame, close to the patient's lips.

These facts may be followed in Fig. 13, in which all possible mixtures of the three gases are represented. At each angle of the *triangle, the gas named is at 100 per cent; along the side opposite,* it is at 0 per cent. Ignitable mixtures are enclosed within the triangular shaded area, those near its boundaries (except its base) being difficult to ignite and detonating feebly or not at all. The mixtures represented by the apex of this area, close to and below the 20 per cent oxygen line, would burn, but not explode.

In Fig. 13, point A represents the mixture in the bag; point B, atmospheric air; point C, expired air (carbon dioxide *being counted*

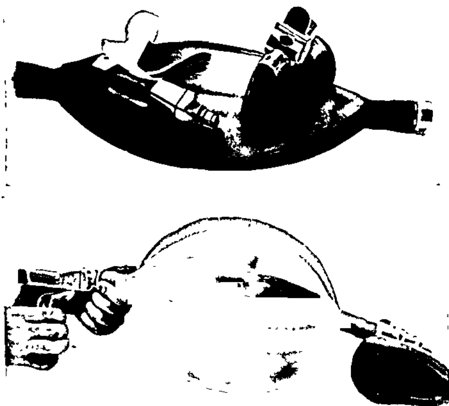


FIG. 14.—Apparatus for administering preset mixtures of cyclopropane, oxygen and nitrogen: Type 1.

dilution were in progress, Hingson was developing non-explosive mixtures with helium as the diluent (Corcoran and Hingson, 1955). The advantage of helium over nitrogen for this purpose is negligible; but Hingson's mixture differed in other respects. My aim was to develop a method of anaesthesia that could safely be used by the 'occasional' anaesthetist for brief administrations: I recommended that administrations should not be prolonged beyond one minute. Hingson had wider applications in view. His purpose was not only to meet the requirements of the 'occasional' anaesthetist but also to provide the trained anaesthetist with a method that could be used in longer cases and non-ambulatory patients. The mixture he finally selected consisted of 40 per cent cyclopropane, 30 per cent oxygen and 30 per cent helium. With this concentration of cyclopropane, overdose, either in adult or child, would be virtually impossible, no matter how long the administration was continued, and with 30 per cent oxygen he claimed that it could be given for six* minutes before the oxygen fell to a physiological level and began to run short (Corcoran and Hingson, 1955). These advantages are considerable and in future work should be weighed against the slight advantage with my mixture of lying a little further from ignitable limits

Apparatus

In reporting his method, Hingson introduced a valuable innovation: the gases for charging the bag were compressed into a pair of small, disposable bulbs, like those in domestic use for charging sodawater siphons with carbon dioxide. Compact apparatus had been devised. Between the face-mask and bag were two inlet valves with piercing needles, one on either side. To charge the bag the bulbs were placed in metal containers, which were then screwed onto the piercing needles, remaining in this position during the administration The mask contained a valve that prevented escape of the gases from the bag. Pressure of the mask on the patient's face opened the valve and allowed the patient to breathe in and out of the bag.

With such an apparatus this method of anaesthesia could be made available in dentists' surgeries and dental clinics, and the way would be open to widespread trial. Previously, the only method of filling the bag was from a Boyle's anaesthesia machine, which is not kept in such places. Hingson's apparatus could be carried in the anaesthetist's pocket. But it was unobtainable in the United Kingdom, and had features that could be improved upon. Using similar bulbs, therefore, I developed in conjunction with Sparklets Limited the apparatus (Type 1) shown in Fig. 14.

* Preliminary experiments with Hingson's mixture suggest that the oxygen would begin to run short in adults after about four minutes.

With this apparatus, the bulbs, which are sealed together, are discharged into the bag through a non-return valve from a gun, after which the gun is detached. The trigger of the gun is elongated to form a lever for pressing the bulbs onto piercing needles in the breech. A two-way stopcock, linking the mask to the bag, shuts off the bag and allows the patient to breathe air while the mask is being applied to the face. The stopcock is then turned and the patient breathes in and out of the bag. If required, a soda-lime canister may be inserted between the stopcock and bag.

This apparatus was developed late in 1955; but it was not put into production because the safety of this method of anaesthesia did not seem to have gained wide acceptance by anaesthetists. Cyclopropane continued to be regarded as too powerful and therefore too dangerous to be placed in the hands of the 'occasional' anaesthetist. Recently, however, the safety and value of the method has been confirmed in this country by Mushin and Thompson (1958) on the basis of more than a hundred administrations with apparatus and bulbs supplied by Hingson. And in a recent disucssion at the Royal Society of Medicine of the problem of anaesthesia for short life-saving operations in the mass casualties of any future war, the method was proposed as a possible solution (Stephens, 1959; Bourne, 1959). In consequence, apparatus and a limited supply of bulbs have now been made available for experimental purposes.

Two types of apparatus are at present on trial: the original apparatus (Type 1) shown in Fig. 14; and the apparatus (Type 2) shown in Fig. 15, in which the charging device, which was designed by British Oxygen Gases Limited, is less bulky and less costly to manufacture than the original one. With the Type 2 apparatus, as with the Type I, the sparklet bulbs are fastened together in pairs, but base to base instead of side by side. The piercing needles are housed in the charging device, one in the cap, the other at the opposite end. The bulbs are placed in the device like a battery in a torch and the cap is then screwed on. They are discharged in sequence* as the cap is screwed home. As with the Type 1 apparatus, the charging device is attached to the bag only for the few seconds needed for discharging the bulbs.

The bulbs at present on trial are loaded to give a somewhat different mixture from that which I have been using in clinical practice (50 per cent cyclopropane, 25 per cent oxygen and 25 per cent nitrogen) The new mixture is virtually the same as Hingson's

* The cyclopropane bulb is more lightly sealed than the oxygen bulb This ensures that the cyclopropane bulb is always the first to be discharged, thus guarding against the existence, even for a moment, of an explosive mixture within the apparatus during the process of charging the bag

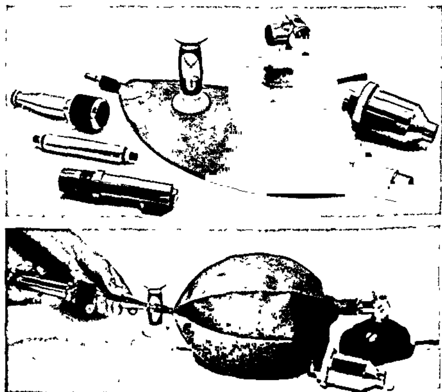


FIG. 15 —Apparatus for administerıng preset mixtures of cyclopropane, oxygen and nitrogen Type 2.

propane used by the method proposed. I report here a study on the lines followed in investigating the respiratory effects of thiopentone (Chapter VIII).

Respiratory Effects of Cyclopropane

In these experiments the bag was filled with 50 per cent cyclopropane and 50 per cent oxygen. When a patient breathes in and out of a six-litre bag filled with this mixture, only the first breath contains cyclopropane at a concentration of 50 per cent. Subsequent breaths become progressively diluted with air from the lungs down to a certain point. The smaller the lungs, the less the dilution, so that the danger of overdose would be greatest in children. In this study, therefore, attention was paid particularly to the respiratory effects in small children.

Material

Thirty-three patients about to undergo operations on the nose or throat were used for the study. The sexes were equally represented. Apart from the local condition the patients were healthy. Eighteen were under 10 years of age: one was 8 months old; three were 4 years old; six were 5 years old; and eight were 6 to 8 years old. Of the remainder, seven were in their second decade. The oldest patient was 61.

Method

The study was made with the patient supine. For pre-anaesthetic medication he was given scopolamine gr. 1/150 (0 4 mg.) or half this dose if he weighed less than 75 pounds (34 Kilos). The six-litre bag was encased in a rigid air-tight box, connected by wide-bore tubing to a Benedict spirometer. A soda-lime canister was not used; carbon dioxide was allowed to accumulate.

As a control, the bag was first filled with oxygen and the respirations of the patient were recorded as he lay awake, breathing in and out of the bag. The bag was then filled with 50 per cent cyclopropane and 50 per cent oxygen and the respirations were recorded as the patient breathed this mixture and became anaesthetised. In every case, the administration was started at the end of a normal exhalation and was continued for about four minutes.

In 22 cases, this administration was immediately followed by an administration of cyclopropane and oxygen from a standard Boyle's machine, so that anaesthesia could be maintained with cyclopropane while the six-litre bag was being emptied and recharged with 50 per cent cyclopropane and 50 per cent oxygen. During the administration from the Boyle's machine, which was usually continued for about

and consists of 40 per cent cyclopropane, 30 per cent oxygen and 30 per cent nitrogen, the total volume delivered from a pair of bulbs being 5·6 litres. One bulb contains the cyclopropane and some of the nitrogen; the other contains the oxygen and the remainder of the nitrogen.

With this mixture, anaesthesia in short cases is indistinguishable clinically from that obtained with the mixture I was previously using; but the higher oxygen content allows administrations to be continued for longer periods before the oxygen begins to run short, and the smaller amount of cyclopropane probably eliminates any possibility of overdose. Experiments are now in progress to determine how long an administration might be continued before the oxygen began to run short, and to test the depth of anaesthesia reached in more prolonged administrations.

With this apparatus we should have at our disposal a method that might help to solve the problem of anaesthesia in at least a considerable proportion of ambulatory patients; and, in my view, the method would be safe with anaesthetists of limited experience. But this is not at present the general view. Perhaps most anaesthetists continue to regard cyclopropane as too powerful to be placed in the hands of the 'occasional' anaesthetist, whatever the method used, their main concern being the possibility of sudden overdose and respiratory arrest. They fear that, if, during induction with cyclopropane at a high concentration, the patient started to inhale deeply, overdose might be reached almost at once, even in a single breath; and indeed a pause in respiration during induction with cyclopropane at a high concentration is a common occurrence. Guedel (1940) believed this pause to be due to momentary overdose; and Hingson explains it on the same basis: "After five to ten breaths there is usually a short period of apnea. It is believed that the momentarily primary high blood concentration of cyclopropane depresses the respiratory center of the brain to this point. The mask is held firmly to the face and after 15 to 20 seconds the breathing will be resumed. The blood has been desaturated of cyclopropane by the body tissues" (Corcoran and Hingson, 1955).

I do not regard this explanation as correct. In earlier work (Bourne, 1952), I gave three reasons for believing, on clinical evidence, that the pause was not due to depression of the respiratory centre: the pause usually occurred at inspiration; when breathing was resumed it was immediately deeper than before the pause; and if the administration was then continued, breathing steadily decreased and became considerably depressed only after about four minutes.

Since it was important to exclude the possibility of sudden overdose, it seemed desirable to study the respiratory effects of cyclo-

18–20, a third tracing (C) shows the patient's respirations during a second administration of 50 per cent cyclopropane from the bag, at the start of which the patient was already anaesthetised.

Apart from a pause in respiration seen in some cases during the first minute of induction, in no patient did respiration become arrested at any stage. Even in the eight month old infant (Fig. 16), respiration was still active after an administration of cyclopropane lasting four minutes. (The irregularities in the respirations during oxygen breathing in this case were due to crying.)

Deep inhalations of cyclopropane did not arrest or unduly depress respiration. This is shown in Fig. 17, in which the respirations of a boy aged 4 are recorded. During the administration of cyclopropane he sneezed twice and in doing so made two inhalations of more than a litre each.

A pause (Figs. 18 and 19) was seen during the first minute of induction in fourteen cases; and in the remaining nineteen cases respiration showed irregularities, with a tendency for pauses to occur (Fig. 20). In every instance, the pause occurred at inspiration, giving a pattern in the spirometer tracing that was entirely different from that seen

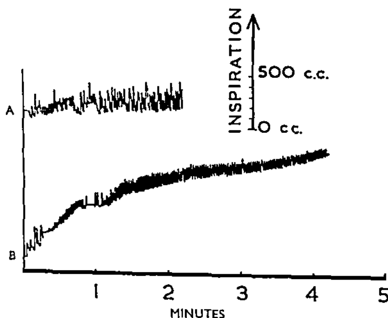


FIG 16—Figures 16–20 show [illegible] of a six-litre bag without C[illegible] taining oxygen; B, during ind[illegible] and 50 per cent oxygen; C (F[illegible] 50 per cent cyclopropane an[illegible] infant, aged 8 months.

four minutes, carbon dioxide was absorbed with soda-lime and the respirations were not recorded. Now, with the patient already anaesthetised with cyclopropane, a second administration of 50 per cent cyclopropane and 50 per cent oxygen was given from the six-litre bag, and the respirations were again recorded. Thus, in each of these 22 cases, three records of respiration were made: A, with the patient awake, breathing oxygen; B, during induction with 50 per cent cyclopropane from the bag; C, during a second administration of 50 per cent cyclopropane from the bag, the patient being already anaesthetised with cyclopropane.

In one case, similar records were made and the same procedure followed, except that the anaesthetic used for maintaining anaesthesia while the bag was being emptied and recharged was not cyclopropane but nitrous oxide. The nitrous oxide administration was continued for nine minutes, which gave time for complete *elimination of the induction dose of cyclopropane. In this case,* therefore, when the second administration of 50 per cent cyclopropane was given from the bag, the patient was under nitrous oxide anaesthesia.

In four cases, the maintenance anaesthetic was thiopentone, the dose being 2½ mg./lb. (5·5 mg /Kilo). In each of these cases, the time interval between completion of the first and the beginning of the second administration of cyclopropane from the bag was greater than six minutes. Throughout this interval, during which the thiopentone was injected, the patient breathed air. Therefore, in these four cases, when the second administration of cyclopropane was given from the bag the patient was under thiopentone anaesthesia.

In fifteen of the twenty-two cases in which the maintenance anaesthetic was cyclopropane, and in two of those in which it was thiopentone, a record was made showing the extent to which respiration recovered spontaneously when the patient was allowed to breathe air for one minute or less after the second administration of cyclopropane from the bag. For this purpose, the stopcock was turned, shutting off the bag and opening the air vent. After the interval of air breathing, the stopcock was turned back and respirations were recorded for a brief interval while the patient again breathed the mixture in the bag.

Results

Typical spirometer tracings are shown in Figs. 16 to 20. In each figure the upper tracing (A) shows the respirations of the patient *awake, the bag containing oxygen. The tracing (B) below this shows* the respirations of the same patient during induction, the bag containing 50 per cent cyclopropane and 50 per cent oxygen. In Figs.

to breathe air for one minute or less resulted in a considerable degree of recovery (Fig. 20). In the fifteen cases in which recovery was tested when cyclopropane had been the maintenance anaesthetic, the improvement in respiration after this short interval of air-breathing was much greater.

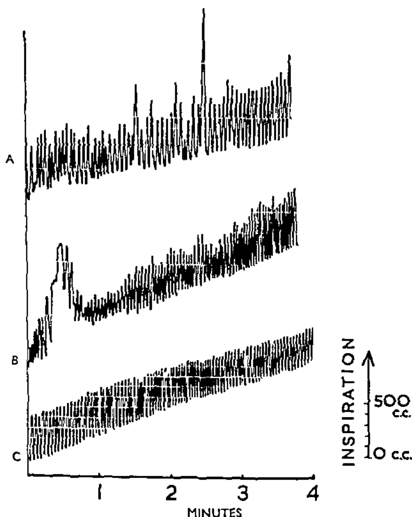


FIG 18—Respirations of a woman, aged 34

(For details, see legend to Fig. 16) Between B and C, anaesthesia, with CO_2 absorption, was maintained for five minutes with cyclopropane from a Boyle's machine.

COMMENT

The pause in respiration that commonly occurs with this method of anaesthesia during the first minute of induction cannot be due to depression of the respiratory centre. For the pause does not occur

with thiopentone (Fig. 10). Of the 27 cases in which the patient was given a second administration of 50 per cent cyclopropane from the bag after anaesthesia had already been established, in none was either pause or irregularity seen during the second administration. This is illustrated in Figs. 18, 19 and 20, where the maintenance anaesthetic was cyclopropane, nitrous oxide and thiopentone respectively.

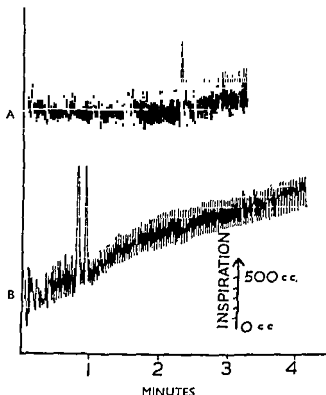


FIG. 17.—Respirations of a boy, aged 4 years. (For details, see legend to Fig. 16). The deep inhalations in B were due to sneezing

In some of the small children, respiration was considerably depressed at the end of the first administration of cyclopropane from the bag. The most marked example in the whole series is shown in Fig. 19. In thirteen children the trachea was intubated at this point. The jaw and larynx were completely relaxed and there was no reaction to this stimulus, showing that anaesthesia was deep.

In the four cases in which the maintenance anaesthetic was thiopentone, depression of respiration during the second administration of cyclopropane became severe. Nevertheless, even when, in these cases, respiration had nearly become arrested, allowing the patient

to breathe air for one minute or less resulted in a considerable degree of recovery (Fig. 20). In the fifteen cases in which recovery was tested when cyclopropane had been the maintenance anaesthetic, the improvement in respiration after this short interval of air-breathing was much greater.

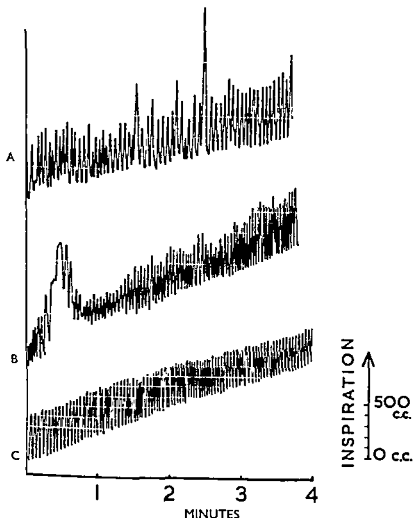


Fig. 18.—Respirations of a woman, aged 34.
(For details, see legend to Fig. 16.) Between B and C, anaesthesia, with CO_2 absorption, was maintained for five minutes with cyclopropane from a Boyle's machine.

Comment

The pause in respiration that commonly occurs with this method of anaesthesia during the first minute of induction cannot be due to depression of the respiratory centre. For the pause does not occur

during an administration to a patient already anaesthetised with cyclopropane, nitrous oxide or thiopentone, when the administration inevitably carries anaesthesia to a deeper level than is reached when it is given to an unanaesthetised patient. The pause should be regarded as a manifestation of the excitement stage of induction. It occurs after consciousness is lost and is commonly associated with muscle spasms and purposeless movements, which will be described later. A similar pause occurring during induction with nitrous oxide was, in fact, described more than 60 years ago by Hewitt: ". . . the so called 'holding the breath' may take place during or immediately

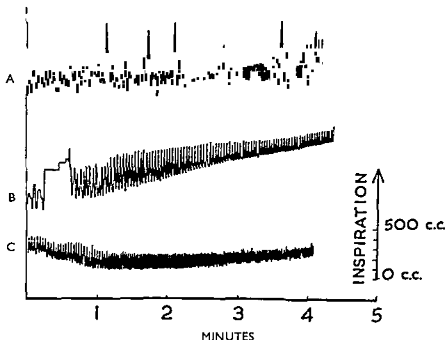


FIG 19.—Respirations of a boy, aged 4 years.
(For details, see legend to Fig 16) Between B and C, anaesthesia was maintained for nine minutes with 80 per cent nitrous oxide on a non-rebreathing system.

after the inhalation of the gases [N_2O with 2%–4% O_2], and thus induce cyanosis. This 'holding the breath' is a misnomer, for the patient is not conscious at the time Certain patients . . . are prone to muscular spasm, and when this spasm affects the chest and abdomen, temporarily arrested breathing necessarily occurs. There is no occasion for alarm in these cases, as the breathing quickly regains its normal rhythm" (Hewitt, 1897*d*).

We may conclude, therefore, that respiratory arrest from overdose is not a danger with 50 per cent cyclopropane given from a six-litre

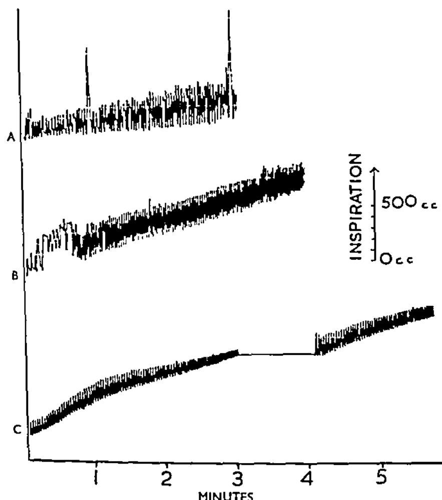


FIG 20.—Respirations of a girl, aged 5 years.
(For details, see legend to Fig 16). Between B and C, the patient breathed air for seven minutes, during which thiopentone, 2·5 mg/pound (5·5 mg/Kilo), was given. In C, the inhalation from the bag was interrupted for one minute, during which the patient breathed air.

bag unless the administration is continued for at least four minutes, and then only in infants or small children. Since administrations of one minute or less are usually sufficient in dental cases, the method would appear to have a wide margin of safety in this field.

It remains for me to review the principal features of anaesthesia with this method.

REVIEW OF 3,000 ADMINISTRATIONS

The account that follows is based on my experience in about 3,000 cases. Detailed records were kept of the first 2,300 cases, of which

1,918 have been briefly reported elsewhere (Bourne, 1951, 1952 and 1954a).

Material

The patients were ambulatory except some of those with serious cardiovascular disease, who were undergoing treatment in hospital. In about 2,500 patients, the operation was extraction of teeth; the remainder were having minor operations of other kinds.

Of the 2,300 cases recorded in detail, in 701 (30%) the patients were children in their first decade; in 322 (14%) they were in their second decade, and in 1,277 (56%) they were aged 20 or older. Thirty-three patients were in their seventies, and eleven were in their eighties The youngest patient was aged seven months, and the oldest was 93. About 40% of the adults were men.

Most of the patients were healthy, but 27 were known to have serious cardiovascular disease: recent coronary thrombosis (6); rheumatic carditis with valvular lesions (5); hypertension, bronchitis and emphysema, with congestive heart failure (2); hypertension and angina of effort, with congestive failure (1); hypertension, with congestive failure (5); hypertension and angina of effort (1); stroke, with hemiplegia (3); congenital heart disease, with cyanosis (3); and chronic constrictive pericarditis, previously treated surgically (1). Two patients, aged 77 and 85, had senile dementia. The series also contained patients with pulmonary tuberculosis, bronchiectasis, asthma, thyrotoxicosis, diabetes, and epilepsy, and pregnant women.

There were 516 patients who, on a previous occasion, had been given nitrous oxide for dental extraction. In 56 of these the attempt to establish anaesthesia with nitrous oxide had failed and the operation had been abandoned. Three girls, aged 3, 13 and 18, and a youth, aged 18, had had syncope and respiratory arrest during the administration of nitrous oxide, followed by delayed recovery of consciousness. There were in addition several small children who screamed and struggled directly they were brought into the treatment room and were so difficult to handle that anaesthesia in the dentist's surgery had not even been attempted.

The number of teeth extracted was recorded in 1,517 cases: in 77 per cent it was three or less; in 18 per cent it was four to six; and in 5 per cent it was more than six.

Method

In the whole series of 3,000 cases, anaesthesia was induced from a six-litre bag charged with 50 per cent cyclopropane. In the first 1,500 dental and in all the non-dental cases, the cyclopropane was

mixed with 50 per cent oxygen; in the remaining 1,000 dental cases it was mixed with 25 per cent oxygen and 25 per cent nitrogen.

Most of the patients had received no pre-anaesthetic medication, but two hundred to three hundred of the dental patients had been given scopolamine* by mouth.

The apparatus used was that shown in Fig. 14, but without the charging device. In place of the inlet valve at the base of the bag was a rubber tube leading to a Boyle's anaesthesia machine, from which the bag was charged. (It will be seen in Fig. 14 that the stopcock contained an expiratory valve, which has been omitted in the Type 2 apparatus shown in Fig. 15.)

(*a*) *Dental Cases*.—The anaesthetic was given with the patient sitting up, except for a few small children and those patients with cardiovascular disease who were under treatment in hospital, who were anaesthetised lying down. The standard procedure was as follows.

The expiratory valve was shut tight and the bag was filled from the anaesthesia machine. After a mouth-prop had been placed between the patient's teeth, the face-mask was applied, covering both mouth and nose. At the end of a normal exhalation, the stopcock was turned, shutting the air-vent and opening a vent between the mask and bag. The patient then breathed in and out of the bag for a period varying between twenty seconds and one and a half minutes, after which the mask was removed, a gauze pack was placed in the mouth behind the teeth that were to be extracted and the extractions were made. A soda-lime canister was not used.

The length of administration depended on the patient's breathing and on the amount of work to be done. When the patient breathed deeply and the extractions were few and easy, as little as six breaths was all that was given from the bag, after which the operation was delayed for a few seconds to allow the full effect of the administration to develop. But when the breathing was slow and shallow or the extractions were numerous or difficult, up to about twenty breaths from the bag were allowed. *Of 460 unselected cases in which the* length of administration was timed, in 90 per cent it did not exceed one minute.

In some of the early cases, in which the anaesthetic was given at a dental teaching hospital and a longer operating time was needed by the dentist for teaching purposes or by the undergraduate dental students who were making the extractions, a somewhat different procedure was followed. In these cases, the flow of cyclopropane

* Scopolamine was given for the purpose of studying its effect on post-anaesthetic nausea and vomiting The study, however, was unsatisfactorily planned and was abandoned.

and oxygen, instead of being stopped when the bag was full, was allowed to continue throughout the administration, each gas entering the bag at a flowrate of 1·5 L./min.; and the expiratory valve was left open to allow the excess gases, mixed with lung air, to escape as the patient exhaled. The administration was continued for two minutes or longer, so that anaesthesia was carried to a deeper level than was reached with the standard procedure and persisted for a longer period after the mask had been removed. When an even longer operating time was needed, as when a tooth was broken during extraction and the roots had to be removed piecemeal, the operation was interrupted when the patient began to respond to the stimulus, the mask was reapplied and a fresh administration from the bag was given for about a minute.

In a few patients early in the series, before the danger of sparks from teeth and dental forceps had become known, anaesthesia was prolonged by giving nitrous oxide with 20 per cent oxygen nasally immediately after the administration of cyclopropane.

In 31 cases in which it was foreseen that the operation would take a considerable time, endotracheal anaesthesia was established. In these cases anaesthesia was induced from the six-litre bag with the patient upright in the dental chair, as in the standard procedure. Suxamethonium was then injected intravenously, and a tube was passed through the nose into the trachea. The throat was packed off, and anaesthesia was continued with cyclopropane and oxygen, the patient remaining upright and carbon dioxide being absorbed in a soda-lime canister. In this way anaesthesia could be maintained indefinitely In one case the operation lasted forty minutes.

Thus in dental cases four methods were used: a single administration from the bag—the standard procedure; a more prolonged and sometimes repeated administration from the bag, the contents being replenished by a continuous flow of gases; a cyclopropane-nitrous oxide and oxygen sequence; and an intubation technique.

No special measures were taken for small children who screamed and struggled as they were carried into the treatment room. They were firmly held, and the mask was applied and the administration begun with the least possible delay. The standard procedure was followed.

(*b*) *Non-Dental Cases.*—For minor operations other than dental, the anaesthetic was given with the patient lying down. In short cases the procedure was the same as the standard procedure in dental cases, except that the administration was continued while the operation was in progress. When anaesthesia became deeper than was necessary, the stopcock was turned, shutting off the bag and opening the air-vent. If the operation had not been completed after about one

minute of air-breathing, the air-vent was again closed and the inhalation from the bag renewed. Occasionally, in longer cases, a soda-lime canister was used. And in a few cases, anaesthesia was maintained with nitrous oxide and oxygen after induction with cyclopropane from the bag.

Results

(*a*) **Loss of Consciousness and Muscle Spasm.**—Loss of consciousness was very rapid. In small children, screaming and struggling ceased abruptly after three or four breaths. Adults questioned afterwards nearly always said that they lost consciousness in three to six breaths, though in some elderly patients unconsciousness came on a little later, presumably due to a sluggish circulation.

After consciousness was lost there occurred a variable degree of purposeless movement and muscle spasm, frequently accompanied by breath-holding. The patient was felt to stiffen under the anaesthetist's hand, often flexing his neck slightly, or slowly turning his head stiffly a little to one side or the other. Sometimes the whole body was involved, usually flexing slightly, with one or several of the extremities becoming slowly and stiffly displaced from the position of rest assumed when the patient took up his position in the chair. Occasionally the movement was considerable, the patient becoming awkwardly displaced in the chair, and in one or two instances the whole body stretched up and became extended in a position of opisthotonos. Then the body relaxed and breathing was resumed. With relaxation, slow clonic movements were frequently seen, particularly in the hands, with 'pill-rolling', reminiscent of Parkinson's disease. Finally, if the administration was continued, relaxation became complete, movement stopped and respiration returned to a normal rhythm. The patient was now in surgical anaesthesia.

During the phase of muscle spasm, the eyes were sometimes open. The pupils were of normal size. The face was pink and slightly flushed; pale patients developed more colour. The pulse as a rule slowed a little and became fuller, which was particularly noticeable in patients in whom it was fast and rather thready at the start of the administration. When the extractions were simple, the administration was often stopped at this stage and the extractions made. Occasionally the patient moved slightly in response to this stimulus, but the movement was purposeless and not enough to interfere with the operation; and the patient invariably said afterwards that he had been completely unconscious.

(*b*) **Signs of Anaesthesia.**—The signs of anaesthesia did not differ from those seen with other inhalational anaesthetics. The entry into

surgical anaesthesia was marked by the onset of muscular relaxation, cessation of movement and resumption of normal respiration. This stage was usually reached within about a minute, but sometimes in adults it took longer. By then the jaw was relaxed and there was no response to the surgical stimulus even though it was strong, as when a difficult extraction was being made or a toe-nail was being removed. As a rule, however, it was not necessary to induce this depth of anaesthesia for simple dental extractions, and then reliance was placed on *the eyelash or eyelid reflex, which is a standard sign with nitrous oxide* anaesthesia in dentistry, or, more commonly, on simply counting the respirations. The bag was watched and usually after six to twelve breaths, depending on their depth and what was being done, the administration was stopped.

(*c*) **Duration of Anaesthesia.**—The standard procedure, that is to say, a single administration from the bag lasting in most cases one *minute or less, uniformly gave about one and a half minutes* of satisfactory operating time after removal of the mask. There followed a period in which the patient was incompletely anaesthetised. He responded to a surgical stimulus, though he remained unconscious for about a further minute. Then, after a short period of confusion, he regained his senses and became rational; and soon he was able to walk with assistance from the chair to the recovery room.

(*d*) **Rate of Recovery.**—The time that elapsed between the beginning of the administration and the moment when the patient left the chair was measured in 352 unselected cases in which the standard procedure had been used. In 86 per cent of cases it was five minutes or less, and in only 6 per cent did it exceed six minutes. This time interval, it should be noted, included induction of anaesthesia, extraction of teeth and recovery to the point of being able to walk. After three or four minutes in the recovery room, the anaesthetic action of the cyclopropane had completely disappeared. In very simple cases and with an experienced dentist and anaesthetist the time could be reduced. On one occasion fifteen children were satisfactorily treated in forty-five minutes.

(*e*) *Failures.—In the whole series of 3,000 cases, there were six* failures, all of which occurred in dental patients in whom nitrous oxide had failed

Two of the failures were in the same patient, a girl, aged 16 when [illegible]

to contend with and the operation was abandoned. It was performed on another day under a different form of anaesthesia, for which the patient was admitted to hospital A year later, she was again given

cyclopropane and again there was profuse salivation. This time she snatched the mask from her face just before losing consciousness.

In three men, aged 21, 26 and 30, there was a sudden outburst of excitement just before consciousness was lost, making it impossible to continue the administration. The man aged 30, who weighed fifteen stone (210 pounds; 95 Kilos) and said he drank sixteen pints (8 litres) of beer a day, was given 200 mg. of thiopentone a few minutes later, followed by a fresh administration of cyclopropane by the standard procedure. The result was entirely satisfactory. The other men were not given thiopentone and the operation was abandoned.

In a man aged 62, no difficulty occurred until consciousness was lost, when muscle spasm developed to an extent that so displaced the patient in the dental chair as to make continuance of the administration and extraction of teeth difficult or impossible. In this case, also, the operation was abandoned.

(*f*) **Complications.**—The only complications of anaesthesia were laryngeal spasm and salivation.

Stridor, without complete closure of the larynx and without cyanosis, was not uncommon. It was noted in 17 cases, but may have occurred more often than this. It was probably no more frequent or severe than that seen with nitrous oxide in dentistry, and it did not cause difficulty or need treatment. Two patients, however, developed laryngeal spasm and became cyanosed. One of them, a man of 38, had rheumatic carditis with valvular lesions. A year previously, he had had signs of early heart failure and had been treated in hospital. In both cases, the only measure taken was to give oxygen. The bag was filled with oxygen and the mask applied to the patient's face. Very soon the spasm gave way, and after a few crowing respirations the patient coughed and the cyanosis disappeared. There were no sequels.

Salivation was noted in ten cases. It was not a prominent feature with this method of anaesthesia and in only one case, that of the girl referred to above, was it profuse. Salivation frequently occurred during recovery from the anaesthetic, but did not give rise to difficulty.

(*g*) **Sequels.**—In the whole series of 3,000 cases there were no deaths, no patient fainted and there was no delay in recovery of consciousness. The only sequels were nausea and vomiting.

In the first 1,000 cases, in many of which anaesthesia was deeper and given for longer periods than with the standard procedure, 33 per cent of the patients were nauseated and 21 per cent retched or vomited. In 526 later cases, in which the standard procedure alone

had been used, 24 per cent of the patients were nauseated and 13 per cent retched or vomited.

Vomiting was never seen during induction or during anaesthesia. It occurred only after consciousness had been regained and when reflexes had recovered sufficiently to prevent danger. In many cases nausea was transient, passing off completely within five minutes or less, but occasionally it persisted for hours. It was accompanied by pallor and sweating.

(*h*) **Patients' Preference for Nitrous Oxide or Cyclopropane.**—Of the 516 patients who had had nitrous oxide on a previous occasion, 16 per cent preferred it to cyclopropane. In every case this was because cyclopropane had made the patient feel sick, whereas nitrous oxide had not done so. Preference for cyclopropane was expressed, often in strong terms, by 70 per cent of the patients, including some who vomited with cyclopropane and had not even been nauseated by nitrous oxide. Their preference was due to the speed and completeness with which consciousness was lost with cyclopropane, and to the relative absence of unpleasant sensations during induction. Many of them said they did not completely lose consciousness with nitrous oxide; they were aware of the extractions; and some of them had felt considerable pain, but were powerless to move. Some had feelings of suffocation or of throbbing or hammering in the head during induction with nitrous oxide, which they did not have with cyclopropane. And a few felt much better after cyclopropane than they had done after nitrous oxide. There remained 14 per cent who were unable to say which anaesthetic they preferred.

COMMENT

Of the four methods used in the dental cases, only the one referred to as the standard procedure is recommended. Extending the period of anaesthesia by interrupting the operation and giving a second administration from the bag is not without risk: when the moment comes to reapply the mask, the mouth contains blood, debris and the gauze pack, and unless care is taken to remove these and to hold the patient's head well forward and facing downwards over his thighs during the second administration, there is danger of respiration becoming obstructed or of blood or other material reaching the trachea. In the hands of an experienced anaesthetist the risk may be small; but with the 'occasional' anaesthetist it should not be taken. Prolonging anaesthesia by giving nitrous oxide and oxygen nasally after induction with cyclopropane, recently recommended by Mushin and Thompson (1958), may reintroduce the risk of ignition by sparks from teeth and dental forceps and result in an explosion. The intubation method, with the patient sitting up in the dental chair, is

difficult and cumbrous: long cases in which intubation is desirable should be handled by trained anaesthetists and with the patient lying down. The standard procedure alone is suitable for use by the 'occasional' anaesthetist.

With the standard procedure, time is limited: the dentist has about one and a half minutes for the operation. But this is less of a drawback than it may at first seem. In Chapter II, I reported that in two-thirds of the teaching hospital cases that I had observed, the dentist needed less than one and a half minutes for the extractions, and that in none of the L.C.C. cases did the operation take more than one minute. Therefore, it seems likely that the length of anaesthesia provided by the standard procedure would be sufficient in a large proportion of the two and a half million cases handled each year in England and Wales. Nevertheless, limitation of the operating time is regarded by exponents of the nitrous oxide method as a serious disadvantage. They claim that with nitrous oxide and oxygen given nasally time is not limited; but in my experience this is not so with the 'occasional' anaesthetist, who is often unable to provide even a few moments of satisfactory anaesthesia with nitrous oxide. Moreover, the possibility of the patient fainting and of the attack escaping detection should perhaps contra-indicate other than very short procedures in patients anaesthetised sitting up. In Chapter V, I concluded that if the cerebral circulation became interrupted as a result of the patient fainting and being kept upright, a period of about two minutes was critical; any longer than this was likely to be followed by severe disturbance of cerebral function and perhaps permanent neuronal damage. Therefore, for everyday use by the 'occasional' anaesthetist, a method that set a limit of one and a half minutes to the operating time might have an advantage over one that encouraged him to try and cater for longer operations. The question that must now be considered is: can fainting occur with the cyclopropane method?

The fact that about 2,500 patients in this series were anaesthetised upright in the dental chair without fainting is not conclusive evidence. If I am correct in my estimate that cases of delayed recovery after nitrous oxide are seen about 500 times a year in the United Kingdom, the incidence of delayed recovery with that anaesthetic would on average be less than 1 in 4,000 cases. This estimate, however, may be too low. In a recent discussion on dental anaesthesia at The Royal Society of Medicine, McConnell (1959), an expert with nitrous oxide of unchallenged authority, said that he meets with cases of delayed recovery with nitrous oxide once or twice a year, or once in every one thousand to two thousand cases. With the much less experienced anaesthetists who do most of the dental work, the incidence of such

cases might be still greater. However, not all cases of delayed recovery with nitrous oxide are due to fainting; some may be due to cardiac syncope from severe lack of oxygen in the lungs, which would not occur with cyclopropane. McConnell stated that this, and not fainting, was the cause in his cases; and in the same discussion, Goldman (1959), who is no less expert with nitrous oxide and apparently also has cases of delayed recovery with it, expressed a similar view: both attributed the sequels to their mistakes—'pushing' the gas more than was advisable, or allowing the airway to become obstructed. They believe that fainting under gas is very rare, if indeed it occurs at all If they are right, a series of 2,500 cases without a faint may not be exceptional. But the evidence given earlier in this monograph leads me to think that they may be mistaken and that many, if not most, of their cases are due to an undetected fainting attack. Moreover, they may have other cases in which fainting, though undetected, is imminent or actually occurs, but in which the patient is laid flat with sufficient promptitude to prevent sequels. In the later cases in my series, when I had become aware of the possibility of fainting, I frequently observed pallor, sighing and a fast thready pulse just before anaesthesia was started, suggesting that the patient was close to fainting. It seems to me, therefore, that fainting may be not uncommon and that, when nitrous oxide was the anaesthetic used, it was to be expected in any series as extensive as the one reported above. If this is so, it is possible that cyclopropane may prevent fainting or cut short an attack. For in my cases, when fainting seemed imminent, I did not lay the patient flat, but proceeded with the administration with the patient upright, and, instead of fainting, the patient always developed a better colour and pulse.

In support of this argument is the fact that the four patients in my series who were known to have had syncope and delayed recovery with nitrous oxide did not faint with cyclopropane. But this evidence also is inconclusive, since there is no certainty that the syncope in their case was due to fainting. Moreover, a patient who faints today under a given stimulus may not do so tomorrow. There is, however, other evidence: light anaesthesia with cyclopropane has been shown experimentally to abolish the fainting reflex (de Wardener *et al.*, 1953). Unfortunately, this again is inconclusive, since the subjects of these experiments were given pre-anaesthetic medication, and thiopentone for induction; and anaesthesia was established before the stimulus for evoking the fainting reflex was applied. The site at which the reflex arc was blocked was not determined. The most likely site is the vaso-motor centre in the brain, which might, in a patient sitting up, be denied the protective influence of cyclopropane by the very act of fainting, if fainting occurred before anaesthesia



FIG. 21.—The extent to which the patient's face is hidden during the administration of nitrous oxide. [Illustration from Wylie and Churchill-Davidson (1960*b*) showing the correct position of the anaesthetist's hands during dental extraction under nitrous oxide.]

was established. For if the attack was sudden and severe at the moment of application of the face mask, the fall in blood pressure might be so precipitous that no blood, and therefore no cyclopropane, reached the brain.

In the present state of knowledge, it would be dangerous to assume that fainting will not occur with the cyclopropane method. Hewitt (1892 and 1907*f*) believed that nitrous oxide could be counted on to ward off an attack when a patient in the dental chair was on the verge of fainting; and indeed, in the study reported in Chapter V, nitrous oxide appeared to have this action in some cases. This mistake should not be repeated. Until the question has been more fully studied, the anaesthetist should be constantly on the watch for fainting, and no less so with cyclopropane than with nitrous oxide. With the cyclopropane method, however, he has the advantage of an uninterrupted view of the patient's face while the extractions are being made, which he is denied with the nitrous oxide method (Fig. 21). He would therefore be less likely to overlook a faint with cyclopropane should it occur.

In non-dental cases, the problem of anaesthesia is less difficult. The patient is recumbent, and therefore fainting is not a risk; and the administration can be continued while the operation is in progress With the mixture used in the non-dental cases—50 per cent cyclopropane and 50 per cent oxygen—there was always sufficient oxygen; but occasionally in small children anaesthesia became deeper than necessary. This was easily corrected by giving air for one minute. But the mixture was explosive and open to objection on that account. With the mixture at present on trial—40 per cent cyclopropane, 30 per cent oxygen and 30 per cent nitrogen—the explosion hazard is eliminated, and there is little risk, even in small children, of anaesthesia becoming too deep; but the operating time is limited owing to the smaller amount of oxygen in the bag. Preliminary measurement suggests that the inspired oxygen begins to fall below physiological levels after about four minutes in adults, and six or seven minutes in children in their first decade. If the administration is stopped at this point, satisfactory anaesthesia will continue for at least a further two minutes, giving a total operating time of about five minutes in adults and nine minutes in small children. Prolonging this time by following the administration of cyclopropane by an administration of nitrous oxide and oxygen re-introduces the explosion hazard and is not recommended. If more time is needed, a second administration of cyclopropane should be given. The bag is emptied and recharged, and the patient is left breathing air until reflex movement is seen, when the face piece is reapplied and anaesthesia continued as before. This may be repeated as often as required and therefore

operations of any length can be catered for. A soda-lime canister is necessary except in short cases; and a sand glass (Fig. 15), like those in domestic use for timing egg-boiling, is a useful adjunct to warn the anaesthetist of the moment when the inspired oxygen is beginning to fall below the 21 per cent of atmospheric air.

The main disadvantage of cyclopropane is post-anaesthetic nausea and vomiting, which occur more frequently with it than they do after brief administrations of nitrous oxide. But this is to some extent offset by other discomforts with nitrous oxide: three out of four of the patients who had experience of both anaesthetics preferred cyclopropane. My experience with patients who have been repeatedly anaesthetised with cyclopropane suggests that if a patient is sick on one occasion he is likely to be so on others. Therefore, if in a given patient nausea is severe and prolonged, he should be anaesthetised on a subsequent occasion in some other way. This appears to be the method's only contra-indication.

With this method of using cyclopropane, whether in dental or non-dental cases, anaesthesia is reduced to its simplest possible terms: the anaesthetist has only to apply the face mask, maintain a clear airway and know how long the administration can be continued. He is not concerned with how much anaesthetic to give; nor does he have to make fine adjustments to the oxygen supply: the amounts are fixed in advance. The method constitutes a return to the simplicity of the original way of using nitrous oxide, as demonstrated in 1868. But whereas with that method the margin of safety was measured in seconds, with the cyclopropane method it is measured in minutes, and whereas with the nitrous oxide method the dentist had at most about forty seconds to complete the extractions, with the cyclopropane method he has more than double this time. The method, therefore, appears to meet the basic requirements: it is simple and effective and has a wide margin of safety

Chapter XI

DISCUSSION

The Danger of Fainting in Dentistry

The main danger with nitrous oxide in dentistry is fainting. However, this explanation of the cerebral complications was not generally accepted by dental anaesthetists when it was published two years ago (Bourne, 1957*b*), and it continues to be questioned. Both McConnell (1959) and Goldman (1959) attribute their cases of delayed recovery to lack of oxygen in the lungs; neither believes that he has ever seen a fainting attack with the anaesthetic. And Macintosh, whose experience with dental anaesthesia is no less extensive than theirs, is reported* as having said that he could not recall having met with a single case of fainting. This can only mean that fainting has been overlooked.

Failure to recognise fainting under gas will be more readily understood if we consider in some detail the parachuting experiments referred to in Chapter VI (p. 43), in which Macintosh himself played a prominent part (Pask *et al.*, 1943). In these experiments, parachute descents were simulated at sea level by administering to volunteers mixtures of oxygen and nitrogen that were physiologically equivalent to breathing air during an actual descent. The subjects were either lying down, sitting or suspended in parachute harness.

When the subject was lying down or sitting, a characteristic picture developed. The subject became cyanosed, and after three-quarters of a minute consciousness was lost. The jaw was clenched. There was considerable turbulence and great muscular rigidity. Breathing was deep and rapid. The pulse was rapid and, in every case, strong.

It is clear from this picture that in all those experiments the circulation remained in a hyperdynamic state, although in one experiment in which he was sitting, the subject appeared 'shocked' after the test and felt sick.

Very different were the reactions when the subject was suspended in parachute harness. The appearances in these experiments were described as "somewhat surprising": "The usual anoxia picture of great muscle spasm, full bounding pulse and vigorous effort to overcome any respiratory obstruction which may develop, with accom-

* Vide the privately circulated Digest Report of a meeting of The Society for the Advancement of Anaesthesia in Dentistry, held on November 20, 1958.

panying stridor, was not seen. Instead, the subject, after quietly losing consciousness, became relaxed and limp." A typical experiment is described in which the subject (P) made a 'descent' from 35,000 feet (10,675 meters). This was simulated by giving at first 4 per cent oxygen and then increasing the oxygen over seven minutes to 9 per cent, when the experiment was terminated. His reactions were as follows. The pulse rate fell from 130, at the end of the first minute, to 65, at three minutes, where it remained until the sixth minute, when it began to increase, reaching 100 at seven minutes. During the bradycardia, the pulse was "very feeble", and respirations fell from 40 to 10 breaths a minute. Just before consciousness was lost, the subject tried to raise himself by pulling on the parachute straps, after which his arms dropped to his sides, his head fell forward and his whole body became limp. Twitching was noticed in the muscles of the left forearm. "For the first time with this subject," *it was recorded*, "*sweating was very noticeable and it actually fell* from the brow." His condition gave rise to great anxiety until after the fifth minute, when he recovered spontaneously.

This description leaves me in little doubt that the subject had fainted during the 'descent'. The slow feeble pulse, the slowing of respiration, the limpness, the profuse sweating, the muscle twitching, and the subject's grave appearance, form a picture that is characteristic of fainting and could not be explained on any other basis. Evidently, however, the faint was overlooked. For in a report on the dangers of parachuting, so important an observation could hardly have been omitted. Yet, although the report made reference to the considerable effect on the circulation of suspension in harness, it was to the feebleness of respiration and its dangers that attention was directed. Fainting was not mentioned.

This experiment provides several points of interest: the possibility that lack of oxygen may have been the stimulus that triggered-off the fainting reflex—emotion is unlikely to have played much part in a subject who was accustomed to such experiments; the fact that the amounts of oxygen given were precisely those used with nitrous oxide in dentistry; and the recovery from fainting that happily took place spontaneously while the subject was still in the upright position —an unusual event. But the point to which I wish particularly to draw attention is that the faint escaped recognition. The fact is that, in the practice of medicine as in everyday life, it is by loss of consciousness and falling that fainting is recognised: the experiment shows how easily fainting may be overlooked, even by trained observers, when loss of consciousness is expected for some other reason and when the body is supported so that it cannot fall.

Here lies the danger in dentistry: fainting under gas is all too

easily overlooked. In the faint recorded in Chapter V, we failed to detect the onset even though we were watching for it; and but for the blood-pressure recording apparatus, the faint would have escaped notice until it had resulted in a very dangerous degree of cerebral anoxia. At that stage, the anaesthetist without knowledge of the possibility of fainting, would almost certainly have misdiagnosed the condition.

For 90 years in the United Kingdom fainting under gas has escaped recognition. In the first year in which nitrous oxide was used in this country, during which about 2,000 administrations were given, at least three cases of fainting may have occurred (pp. 5 and 40). One of the patients, as I have related, was sent home in a carriage while still in stupor. Today we may ask how many thousands of patients since then have been sent home in stupor, and how many brains have been damaged.

The Danger of Fainting in Surgical Practice

The danger of fainting that came to light through my investigation of dental anaesthesia may have grave significance throughout the whole field of surgery. Its possible importance in this field justifies mention here and suggests an urgent need for further investigation.

It is a principle of surgical nursing for patients, especially if they are elderly, to be propped up in bed after operation, particularly after operations on the abdomen, thorax, breast, thyroid, or prostate. Nurses soon learn that if this is done too soon the patient may immediately pass into a state of 'shock', with pallor, sweating, and sometimes loss of consciousness. The propping-up process is therefore delayed and often done in stages; but by nine or ten o'clock at night most of the patients operated on during the day are upright.

Delay in propping patients up, however, does not prevent the onset of 'shock', which may develop in patients in whom it is least expected and after they have been upright several hours. Two fatal cases have come to my notice, in the second of which I myself had given the anaesthetic; and I have undoubtedly had other cases before I became aware of this danger:

> A very nervous woman of 28, who had had an abdominal operation the previous day, was noticed in the early morning to be extremely pale, sweating, and semi-comatose. She was immediately laid flat and attempts were made to resuscitate her. But she did not regain consciousness, and died three hours later (Crane, 1957).

> A woman of 79 was anaesthetised during the afternoon for the removal of her gall-bladder. She regained consciousness before leaving the operating-theatre, and at nightfall her condition was completely satisfactory. She was propped upright and given morphine. During the

night she complained of pain and was again given morphine. In the early morning the night nurses, making beds, found her 'asleep', pale and sweating profusely. They made her bed, taking care not to disturb her. Half an hour later she was noticed to be dead.

At necropsy no lesion was found in either patient to account for death. In the older woman, the heart-muscle and its vessels were remarkably healthy. Death was attributed to surgical shock.

The occurrence of 'shock' in patients propped up in bed after operation is probably familiar to every nurse who has worked in surgical wards. A sister with extensive experience of ear, nose and throat cases could recall two recent instances of considerable severity and several that were less severe (Brown, 1959). The severe cases were as follows:

A mongol girl, aged 13, had tonsils and adenoids removed in the morning Operation, anaesthesia and recovery of consciousness after anaesthesia were uneventful. Two hours after operation she was restless and insisted on sitting up. She was allowed to do so and was given papaveretum, gr. 1/6 (10 mg.) Six hours after operation she was sitting up doing a jig-saw puzzle. She was becoming restless, and the dose of papaveretum was repeated An hour later she was found to be 'asleep'. She was laid back on pillows still upright Half an hour later she was found to be grey, sweating, pulseless and completely unrousable. Breathing was stertorous and soon ceased. At that moment she was thought to be dead. She was quickly laid flat and given artificial respiration and oxygen The face became flushed and spontaneous respiration returned, but she remained completely unconscious She continued to be unconscious for about twenty minutes and was then stuporous for a further two hours, after which she recovered.

A woman of 30 had a radical antrostomy in the morning Here again, operation, anaesthesia and recovery were uneventful. Two hours after operation she was fully conscious. She rinsed out her mouth and was propped up in bed Six hours after operation she said she felt faint Her pulse became slow and feeble, and she lost consciousness. The house surgeon was sent for; meanwhile, she was left upright and given oxygen (The giving of oxygen as the first measure to be taken in post-operative 'shock' appears to be standard teaching in nursing) When the house surgeon came five minutes later, she was laid flat. She had marked pallor and sweating She remained unconscious fifteen to twenty minutes and was then stuporous. Next morning she was still somewhat dazed and had no memory of the events of the previous day. In the afternoon she was propped up again, but after half an hour she again became 'shocked' and lost consciousness, with marked pallor and sweating, and a slow feeble pulse. This time she was laid flat at once. Consciousness returned within five minutes and she was dazed not longer than fifteen minutes

The sister who described these cases said it was common for patients to ask to be propped up after operation and later to say they felt dizzy and ask to be laid flat again. 'Shock', she said, was very commonly seen in patients admitted to the wards because of severe nose-bleeding, for which the first aid treatment was to place the patient upright in bed, with a cork between his teeth, and allow him to hold a bowl to catch the blood (Trotter's method). She had learned from experience never to leave these patients unwatched, so likely were they to become 'shocked', with pallor, sweating and loss of consciousness. They were laid flat the moment the first sign of 'shock' appeared, though its onset was sometimes delayed for hours.

It seems probable that this form of 'shock' after operation is nothing but a common fainting-attack, many factors being present to evoke the fainting-reflex (including the upright position, loss of blood at operation, pain, morphine, nausea, and heat from hot bottles and blankets). If this is correct, the same danger arises here as in dental or other cases in which the body is supported in the upright position during fainting, so that it cannot fall. In surgical practice, however, the danger is especially great, since there must inevitably be considerable periods during the night when any given patient is not under direct observation. Moreover, in a dimly lighted ward, fainting might be mistaken for normal sleep.

Fainting may have accounted for some at least of the nine cases reported by Hunter (1949) under the title: "A new type of encephalopathy after general anaesthesia". In these cases, the patient made a normal recovery from operation and anaesthesia, but six to eighteen hours later lapsed into profound dementia or coma and died within the next few days. In seven of the cases the operation was radical mastectomy, in one it was thyroidectomy, and in one, abdomino-perineal resection of rectum—operations in which there is considerable loss of blood and after which it is customary for the patient to be propped up in bed. Hunter believed the condition to be due to some form of embolism, though there was no evidence of it at necropsy. Both the clinical features he described and the bilateral focal necrosis found in the cerebral cortex on histological examination were entirely consistent with severe cerebral anoxia.

Identical findings, both clinical and histological, were reported by Wolf and Siris (1937) in three patients operated on in the sitting position for trigeminal neuralgia. They were undergoing section of the sensory root of the fifth cranial nerve under local anaesthesia. All three patients had a precipitous fall in blood pressure and lost consciousness during the operation, one of them soon after the injection of the local anaesthetic. Loss of consciousness was accompanied by pallor and stertorous breathing, and in one case, it was

noted, "the operation was unusually easy and bloodless". Stimulants and vaso-pressor drugs were given. The patients survived the operation, but were in a state of profound dementia or coma until their death within the next few days. The authors attributed the brain lesions to cerebral anaemia due to hypotension and the upright position, and they thought that "psychic trauma" might have been a contributory factor.

Fainting may also have accounted for some of the cases referred to by Bedford (1955), whose study has serious implications. He found that in no less than 10 per cent of a large group of elderly patients who had undergone operations, there was a prima-facie case for the allegation of relatives that the patient had "never been the same since his operation". They had, in fact, various degrees of dementia. In most of them the dementia was minor, but in some it was extreme. Their state, he noted, was "strikingly similar to that of young people surviving several minutes of cardiac arrest".

I do not wish to imply that all disturbances of cerebral function after operation are due to a low-blood-pressure state, or that a low-blood-pressure state is always due to fainting. Nevertheless, it seems to me that fainting may be a frequent cause of these catastrophes. Elderly patients who, following operation, lapse into coma and die as a result of having fainted would probably be thought to have had a stroke.

Is the Upright Position Necessary?

In surgical practice the upright position seems difficult to justify. For the main purpose of propping patients up, as far as I can discover, is to prevent postoperative pulmonary complications, of which the most serious is atelectasis due to inability to cough up sputum. But Brock (1936) has pointed out that productive coughing is difficult in the sitting posture, the lateral or semi-prone position being best for this purpose. He recommended that at least three times a day all pillows should be removed and the patient placed in the lateral position to let him clear his lungs. If this is so, should not the upright position be reserved for cases in which there are real indications for it, and its routine use be abandoned?

In dental practice the need for the upright position during nitrous-oxide anaesthesia was challenged in America in the earliest years of its use, when Morrison (1873), referring to the danger of syncope, wrote: "Many of our best surgeons will not, under any circumstances, administer an anaesthetic in the erect posture, and in this respect the present practice of dentists is deemed reckless by them, and justly too, for there is no valid excuse for it. . . . Any dentist neglecting to

place his patient in a horizontal position will fail to acquit himself of blame in case of a death from syncope . . . This position should be secured on the first symptoms of fainting. . . ."

In dental and surgical practice we should take notice of the warning given more than a century ago by Benjamin Ward Richardson (1854). Referring to fainting in relation to posture, he wrote: "Death absolutely would indeed soon occur if the erect position of the body continued . . . but . . . the body falls or is laid down in the horizontal position, and by this simple act the conditions previously existing are entirely changed. . . ."

Prevention and Treatment of Anoxia in Dentistry

Prevention of severe anoxia must await the introduction into everyday practice of safe and satisfactory methods of giving anaesthesia for dental extraction without restriction of oxygen and, if necessary, with the patient lying down. Meanwhile, many cases could be prevented if dentists and dental anaesthetists were warned of the danger of fainting. They should be on the look-out for its signs: pallor, sweating, sterterous and irregular breathing or cessation of respiration, twitching of muscles, dilatation of the pupils and a pulse that is absent, or else feeble and, as a rule, slow. If any one of these appears, work should stop immediately and the patient should be laid down in the horizontal position without a moment's delay. On no account should oxygen or artificial respiration be given until the patient is horizontal.

On no account, also, should the patient be sent home in stupor when recovery is delayed. After anoxia, patients often have a remission and then relapse. A partially lucid interval is not uncommon in such cases. In one of Steegmann's (1939) cases the patient relapsed and died after having recovered sufficiently to be discharged from hospital; and Courville *et al.* (1953) described a patient who regained consciousness and talked half an hour after a nitrous-oxide anoxia, but became permanently spastic and demented.

The patient should therefore be kept flat and sent to hospital, where he should be nursed in this position and remain under observation until he has completely recovered. Benefit has been obtained from intravenous injections of hypertonic solutions of sucrose (Argent and Cope, 1956; Raison, 1957).

Future Practice

The danger and disadvantages of the nitrous oxide method should be acknowledged. To gloss over the sequels or attribute them entirely to errors in the use of the method leads to distortion of facts and suppression of data. Improved training of anaesthetists or

increased care in using nitrous oxide would not eliminate the danger. The method itself is faulty.

In this monograph, attention has been directed mainly to cerebral damage, with fainting rather than restriction of oxygen as the main cause. Little has been said about mortality. Immediate death under anaesthesia—death actually taking place in the dental surgery or clinic—is probably rare. For the years 1948 and 1949, the Registrar-General's review for England and Wales give 13 and 20, respectively, as the number of deaths "associated with anaesthesia" in the treatment of diseases of the teeth and gums (Registrar-General, *1953a*). In the same years there were 39 and 24 deaths, respectively, all operations included, "under or associated with" anaesthesia, where nitrous oxide was the sole anaesthetic used (Registrar-General, 1953*b*). And in the period 1950–52, there were 49 such deaths (Registrar-General, 1955). Since nowadays nitrous oxide is seldom if ever used as a sole anaesthetic in patients admitted to hospital, all these deaths may have been in ambulatory patients. There may, however, have been other deaths resulting from nitrous-oxide anoxia in which the fatal issue was delayed days or weeks and was finally attributed to some other cause. The figures, therefore, may not be comprehensive.

Not only for its danger, however, should the nitrous oxide method be regarded as unsatisfactory. Were it easy to use, effective, more acceptable to the patient than any other, were it to be counted on at least to abolish pain, a case might be made out for its continued use. But it is none of these. The fact should be acknowledged also that the anaesthesia it provides is mainly a product of controlled hypoxia, and the control is remote and imprecise at that. For, between the oxygen tension in the brain, which determines the effect, and the amount of oxygen supplied to the lungs, which is *supposedly* under control, there intervene in the respiratory and circulatory systems physiological variables that the anaesthetist is unable to control. I use the word "*supposedly*" because the amount of oxygen supplied to the lungs is controlled through the gas machine; and this may be grossly inaccurate (Appendix F).

What, then, of future practice? I have given reasons for thinking that cyclopropane, used as described in Chapter X, might satisfy the requirements in a high proportion of the dental and perhaps all the non-dental cases Whether fainting is a risk with cyclopropane in *patients sitting up in the dental chair remains to be determined.* Meanwhile, should a patient show any sign of being disposed to faint, he should be anaesthetised supine and, if the upright position is considered necessary, propped up only when anaesthesia has been established.

Endotracheal Anaesthesia

There remains to be considered the residue of dental patients who cannot be dealt with by the method referred to in the preceding paragraph. These are mainly patients for whom a longer operating time is needed.

The solution here is endotracheal anaesthesia. For this a trained anaesthetist is required, and he should be equipped with all the apparatus needed for major anaesthetic procedures. The anaesthetic should be given with the patient lying down. A cuffed endotracheal tube should be used and should be passed through the nose to leave the dentist a clear field. As an additional safeguard, the throat should be lightly packed, and suction apparatus should be available. The actual technique of anaesthesia will depend to some extent on the anaesthetist's preference. With trained anaesthetists the selection of method can be left in their hands. As previously stated, I have found the method reported in Chapter VII helpful, though induction with thiopentone instead of cyclopropane is preferred by patients and is easier to handle.

Amongst other possible methods are the following:

1. Induction with 50 per cent cyclopropane and 50 per cent oxygen to a depth that allows easy intubation, after which anaesthesia is continued with nitrous oxide and oxygen (8 litres and 2 litres per minute). In adults, consciousness may be abolished immediately before induction by injecting thiopentone in a dose of about 1 mg. per pound body weight (2·2 mg./Kilo).

This method is useful in children and could be used satisfactorily in adults if the cyclopropane, like the oxygen, rotameter were calibrated for flowrates up to five litres a minute. Recovery is more rapid with it than with any other method. Apart from nausea—which probably occurs with about equal frequency with all the inhalational anaesthetics, including nitrous oxide, when given for more than a few minutes—the patient recovers completely, even after a long administration, within ten minutes.

The main disadvantage is the explosion hazard. The patient's lungs contain an explosive mixture during induction and for some time after the cyclopropane has been withdrawn. Other disadvantages arise from the cost of cyclopropane and the low potency of nitrous oxide: the amount of cyclopropane needed in adults entails considerable expense at the present cost of the anaesthetic; and patients who have developed tolerance to central nervous system depressants begin to 'wake up' three or four minutes after the cyclopropane has been withdrawn, necessitating the use of a supplement. Thiopentone or halothane may be the most suitable.

2. Induction with thiopentone and suxamethonium, followed by inflation of the lungs with oxygen and intubation, after which anaesthesia is maintained with nitrous oxide and oxygen (8 litres and 2 litres per minute). In 37 consecutive cases, including patients with a high degree of tolerance, as little as 1·5 mg. of thiopentone and 0·33 mg. of suxamethonium per pound body weight (3·3 mg. and 0·73 mg. per Kilo, respectively) were found to be sufficient for induction.

This method, which broadly follows the lines suggested many years ago (Bourne, 1947), when curare was the only relaxant available, is the simplest and safest of all, and one that is familiar to anaesthetists from everyday use in in-patients. Recovery is rapid if the amount of thiopentone is kept to a minimum; but the anaesthetist should bear in mind that, if good operating conditions are maintained by repeated injections of suxamethonium, there is danger in patients with a high degree of tolerance of consciousness being regained while the operation and anaesthesia are still in progress. A supplement should be used in such cases.

The disadvantage of this method is the muscle stiffness and pain that often follow the use of suxamethonium and may incapacitate the patient for two or three days (Bourne *et al.*, 1952; Churchill-Davidson, 1954). This is a serious drawback, and there is clearly a great need for a short-acting muscle relaxant of the non-depolarising type, which Bovet, as long ago as 1954, stated in a personal communication should not be difficult to synthesise.

3. A method similar to the one just described, except that gallamine replaces suxamethonium as the muscle relaxant. The gallamine may be drawn into the same syringe as the thiopentone and the two drugs injected together, the dose of gallamine being about 0·75 mg. per pound (1·7 mg/Kilo). If the minimal dose of thiopentone is used, the lungs should be inflated, not with oxygen, but with nitrous oxide and oxygen (8 litres and 2 litres per minute) while the full effect of the relaxant is developing, to ensure unconsciousness during intubation. Anaesthesia may then be continued with nitrous oxide and oxygen at the same flowrates, using artificial respiration and carbon dioxide absorption. At the end of the operation, neostigmine will be needed to counter the effect of the gallamine.

This method is particularly well suited for longer operations, as for example in patients whose teeth have been neglected and who need conservative treatment in addition to extractions. A difficulty arises from the fact that the gallamine will mask evidence of tolerance, and therefore consciousness might be regained during the operation with scarcely any sign to warn the anaesthetist. Very often this possibility can be excluded by a few simple questions put to the

patient before the anaesthetic is given. If not, it is better to use a larger dose of thiopentone, perhaps 2·0 to 2·5 mg./lb. (4·4 to 5·5 mg./Kilo), which has the additional advantage of allowing the lungs to be inflated with oxygen prior to intubation.

Safeguards against Vomiting

Vomiting is a constant danger in ambulatory patients. The usual rule of insisting on an interval of four hours between the patient's taking food or fluids and his being given an anaesthetic is by no means an adequate safeguard. I have seen two patients, who were badly burned soon after a heavy meal, vomit the meal completely undigested thirteen hours later; and a girl of 4 admitted to hospital the previous day for removal of tonsils and adenoids vomited during recovery from ether anaesthesia about half a pint of semi-solid 'light' breakfast that she had been given in the ward seven hours previously.

The safest rule is for the patient on the day of operation to have nothing that would not go through a hair sieve; and since milk curdles in the stomach, it should be allowed only in small quantity, such as would be used in one or two cups of tea. Water-clear fruit-flavoured drinks containing ordinary sugar or glucose form the best diet for the day of operation. But during the four hours prior to anaesthesia, the patient should have nothing whatever, not even water. Ambulatory patients for whom an operation under general anaesthesia has been planned for some future date should be given a copy of these rules set down in print, and the danger that might result from their being disregarded should be explained. A statement that the instructions have been fully complied with might be included in the consent form that the patient signs immediately before operation.

Patients who have not been prepared in this way should be regarded as at risk from vomiting. Here, the only safe thing to do is to carry out induction with the patient on his left side and tilted head downwards. The thiopentone-suxamethonium method should be used, and it adds to the safety if the patient is breathing oxygen while the anaesthetic is being given. As soon as the tube is in place and the cuff inflated the danger is passed, and he may then be put in any position. When the operation is finished, the patient should again be turned on his side. The tube should be left in place with the cuff inflated until the patient is making purposeful movements and consciousness has practically returned.

Premedication

Little or no pre-anaesthetic medication is needed, although without it secretions in the patient's mouth and pharynx may be trouble-

some. They can be decreased by giving scopolamine, which may also help to lessen post-operative nausea. This can be given by mouth in tablet form in a dose of gr. 1/150 (0·4 mg.), or half this amount for children in their first decade.

At present, endotracheal anaesthesia is considered to require admission to hospital for one, or even two nights. This would be entirely unnecessary if provision were made for its use in ambulatory patients. Clinics should be furnished for the purpose, with recovery rooms in which patients could rest until they were ready to be escorted home. The clinics should be fully equipped both for dentistry and for anaesthesia and should, perhaps, be open to use by any dentist in the locality. Their cost might compare favourably with the expense incurred through the unsuccessful surgery and the catastrophies that arise under existing arrangements. For with proper facilities, anaesthesia for dental operations need have neither mortality nor serious morbidity.

Today, the facilities for giving anaesthesia to ambulatory dental patients and the method almost universally used are Victorian. From time to time a new gas machine is introduced. This may give a semblance of progress: what is needed is an altogether fresh approach.

Chapter XII

SUMMARY

EACH year, in England and Wales, about two and a half million administrations of general anaesthesia are given to ambulatory patients for extraction of teeth. In at least three-quarters of the cases the anaesthetic used is nitrous oxide.

To give nitrous oxide to a patient sitting up in the dental chair has always been considered safe. Information obtained from a random sample of nearly 400 dentists in the United Kingdom showed that it was not safe. Administration of the anaesthetic was not uncommonly followed by severe disturbance of cerebral function, the patient remaining unconscious or stuporous, in the less serious cases for at least half an hour, and in the more serious cases for days or even weeks. The possibility could not be excluded that even in the less serious cases the brain had received permanent neuronal damage.

About one-third of the 15,000 dentists in the United Kingdom had met with such cases. The condition was seen in dental practice in this country in at least 500 cases a year.

Analysis of 99 non-fatal, and 9 fatal, cases suggested that the cause of the condition was severe cerebral anoxia, resulting from patients being kept upright during syncope, and possibly exacerbated by restriction of oxygen in the anaesthetic mixture. In many cases the syncope appeared to have taken the form of a common fainting attack.

This hypothesis was confirmed in a laboratory study of the circulation of patients under nitrous oxide anaesthesia in the dental chair. Fifteen patients were studied, one of whom fainted during the administration of gas. His blood pressure fell to a level at which, in the upright position, cerebral circulation comes to a standstill. His brain was therefore in the same danger as if his heart had stopped beating.

Fainting under gas is extremely difficult to recognise. It has, in fact, been overlooked throughout the 90 years during which nitrous oxide has been used in this country. Difficulty in recognising fainting occurs whenever loss of consciousness is expected for some other reason and the body is supported so that it cannot fall. Therefore, the same danger arises in patients propped up in bed after surgical operations, when many factors may be present to trigger-off the fainting reflex and when loss of consciousness may be mistaken for normal sleep.

We may conclude that the upright position of the patient in the dental chair during the administration of gas, or propped up in bed after a surgical operation, is dangerous: the patient may faint, and unless the attack is noticed at once and the patient is laid down in the horizontal position, he may die or his brain may be permanently damaged.

Fainting is not the only cause of severe cerebral anoxia with nitrous oxide in dentistry· restriction of oxygen in the anaesthetic mixture is an important contributory factor. It has been shown by other workers to result in death or permanent spasticity and dementia in patients anaesthetised lying down. The use of nitrous oxide with restricted amounts of oxygen should be abandoned in work with ambulatory patients as it has been in all other fields of anaesthesia.

The potency of nitrous oxide was studied in 200 patients to test the possibility of modifying the method by using nitrous oxide with an atmospheric amount of oxygen. The study showed wide individual variation in response, which was found to be due to the development of tolerance from the habitual use of alcohol or possibly other central nervous system depressants. In susceptible patients—those with no tolerance—nitrous oxide was capable of inducing a state bordering on anaesthesia, but induction took ten minutes. Patients with a high degree of tolerance might not even lose consciousness and could experience pain. In the hands of the experienced anaesthetist, using intubation, relaxants and, when necessary, supplements, nitrous oxide might be put to good use in ambulatory patients. For the 'occasional' anaesthetist it was unsuitable.

As a substitute for nitrous oxide in ambulatory work, intravenous anaesthesia, if its use became general, would be unsatisfactory and dangerous.

In the selection of an alternative inhalational agent, consideration should be given to the factors governing the speed of uptake and elimination of inert gases by the body, which in turn govern the speed of induction and recovery with an anaesthetic. Chief of these is the anaesthetic's solubility in blood. Low blood-solubility favours rapid induction and recovery, whereas with an anaesthetic of high blood-solubility, induction and recovery are slow. We should therefore select an anaesthetic of low blood-solubility.

With an anaesthetic of low blood-solubility, any alteration in inspired tension is quickly reflected in the tissues. That is why induction and recovery are rapid. If an anaesthetic of low blood-solubility happens also to be very powerful, a gross overdose might be given and result in lethal tensions in the brain and heart within a few breaths. To be safe, therefore, an anaesthetic of low blood-solubility should not be too powerful

Of the eight anaesthetics at our command, cyclopropane meets the requirements more nearly than any other. Its blood-solubility is lower than that of any other; and in the scale of potencies it comes next to nitrous oxide. It is strong enough to be effective, but not so strong that anaesthesia with it might become uncontrollable. For our purpose, its potency could hardly be improved upon.

The explosion hazard with cyclopropane can be eliminated by giving the anaesthetic from a six-litre bag in a preset mixture with oxygen and nitrogen. Used in this way, it would be safe in the hands of the 'occasional' anaesthetist and would meet the requirements in a high proportion of dental, and, perhaps, all non-dental, cases. In the remaining dental cases, the patient should be given the benefit of endotracheal anaesthesia.

Clinics should be set up and made available to all dentists for the treatment of their ambulatory patients lying down on an operating table and under endotracheal anaesthesia administered by an experienced anaesthetist.

APPENDIX A

A NOTE ON FAINTING

The mechanism of the common fainting attack is still somewhat obscure. Certain facts, however, have been established but do not appear to be widely known. My purpose here is to outline the main features of the condition, indicating sources to which the reader may refer for detailed information. The account that follows is based mainly on an analysis of syncope by Sharpey-Schafer (1956), and on reviews on fainting by Barcroft and Swan (1953) and by Edholm (1952)—authors who themselves have made considerable contributions to this field of knowledge.

Nomenclature

Fainting and Syncope are often used as though they were synonymous. Their meanings should be kept distinct. *Syncope* has been defined as loss of consciousness due to an acute decrease in cerebral blood flow (Sharpey-Schafer, 1956). Cerebral blood flow depends mainly on arterial blood pressure, and when this falls below 50 mm Hg for a few seconds syncope results. Since arterial blood pressure depends directly on cardiac output and total peripheral resistance, syncope will occur whenever there is a large decrease in either of these without compensating increase in the other, or when both decrease simultaneously.

Syncope, therefore, is a term that may be used in relation to a wide variety of conditions: the Stokes-Adams attack, acute myocardial infarction, paroxysmal tachycardia with heart rates above 180, paroxysmal ventricular fibrillation, massive pulmonary embolism, primary pulmonary hypertension, carotid sinus syncope, the valsalva manoeuvre and cough syncope, gravity shock in animals, and the common fainting attack in man. *Syncope* is thus a generic term: *fainting* is one of its specific causes.

Throughout this monograph *fainting* has been used to denote the common fainting attack and no other form of syncope. Other names for it are *vasovagal faint*, *vasovagal syncope* or *vasovagal syndrome* (Cotton and Lewis, 1918, Lewis, 1932), and *vasodepressor syncope* (Engel, 1950*d*).

Definition of Fainting.—Fainting is a reflex peculiar to man, characterised by an acute decrease in blood-pressure and heart rate, with pallor, sweating and, when fully developed, loss of consciousness and muscle tone.

Aetiology

(*a*) *Predisposing factors*.—Fainting affects the young especially, but by no means exclusively, and people who are out of condition, in poor health or convalescent. Other predisposing factors are anxiety or emotional stress, undernutrition, fasting, fatigue, anaemia, carbon monoxide poisoning, hard exercise, and a hot environment (Lewis, 1932; Weiss, 1935*d*; Haldane and Priestley, 1935). Fainting is provoked most readily in the upright position, less so in the sitting position, and with difficulty in a subject lying down.

Fainting can occur also in people in robust health, and it is impossible to predict which subject will faint under a given stimulus. Any healthy person can be made to faint; but fainting is rare in patients with heart disease, though they may be prone to syncope of other kinds. In actual heart failure, fainting appears to be impossible (Sharpey-Schafer *et al.* 1958).

(*b*) *Precipitating factors*.—The chief cause of fainting is haemorrhage, which may, as will be seen later, be the basis on which the reflex depends. The loss of one litre of blood will cause fainting in more than 50 per cent of normal people, and if enough blood is withdrawn, any healthy person can be made to faint. Other factors that may trigger-off the reflex are: emotion, such as fear, or the feeling aroused in some people by the sight of blood; pain; prolonged standing at attention; maintenance of the upright position with weight off the feet, particularly after strenuous exercise or after the administration of a vaso-dilating drug, such as alcohol or sodium nitrite; spinal anaesthesia; the breathing of atmospheres poor in oxygen; nausea; certain drugs that are liable to produce nausea, such as morphine and its derivatives, particularly apomorphine; and the supine position in late pregnancy (Barcroft and Edholm, 1945; etc.).

When two or more precipitating factors are applied simultaneously, their effects are additive. Thus fainting was induced in three out of thirteen volunteers by the administration of 7 per cent to 10 per cent oxygen in nitrogen; but when this stimulus was applied to the same subjects after the simulated loss of an amount of blood that only rarely causes fainting, ten of them fainted (Anderson *et al.* 1946). There is, therefore, little wonder that fainting occurs with nitrous oxide anaesthesia in the dental chair, since the patient may present a multiplicity of both predisposing and precipitating factors, the latter including fear, pain, nausea and the breathing of gas mixtures poor in oxygen. In the patient propped up in bed after an operation the number of predisposing and precipitating factors may be formidable.

Symptoms and Signs

The onset of fainting may be so abrupt that there is little to warn onlookers or the subject himself. As a rule, however, the attack is preceded by yawning, sighing, pallor, and sweating. This may be accompanied by nausea, abdominal discomfort and a desire to defaecate. Vision then becomes disturbed; the subject feels dizzy; consciousness is lost, and he falls to the ground. This is followed by a momentary facial flush and then extreme pallor and profuse sweating.

At the height of the attack, breathing may be shallow and irregular, and sometimes jerky and stertorous. The pupil is dilated and the appearance death-like: there is no other condition, not even the deepest coma, that so closely resembles death (Weiss, 1935*e*). Small convulsive movements or muscle twitchings are common, and, more rarely, even a normal person not subject to epilepsy may have a full-blown epileptic attack.

The heart rate always decreases in fainting. Edholm (1952) observed a decrease in every one of 120 experimentally induced faints. But if the heart rate prior to the faint is fast and has not been observed, the decrease may be missed, since it may not give rise to a noticeable bradycardia. In a severe attack, there may be complete cardiac arrest lasting many seconds.

The blood pressure in fainting falls precipitously. In the faint recorded in Chapter V it reached as low as 30/15 mm. Hg. It is interesting to note that when the heart is arrested for about twenty seconds in a Stokes-Adams attack or following the intravenous injection of acetylcholine, the arterial blood pressure does not fall to zero but remains constant at 20 to 25 mm. Hg (Barlow and Howarth, 1953). Presumably, however, blood flow everywhere comes to a halt.

When the subject is not prevented from falling into the horizontal position, consciousness is regained almost immediately. The abolition of muscle power that makes him fall provides a natural safeguard to the brain, as many workers have pointed out. Convulsions, when they occur, give further help in restoring the circulation. However, even when he falls and regains consciousness at once, pallor and nausea may continue, and for an hour or more he may remain tremulous and weak, sometimes with severe headache. It is important to bear in mind that once fainting has occurred the tendency for the subject to faint again if he is raised into the sitting position may persist for several hours.

If falling is prevented and the subject remains upright, any one of four things may happen he may recover spontaneously from the faint (this is unusual); he may recover for a moment and then faint

again, perhaps repeatedly; he may continue in the faint, perhaps getting worse (this is the most likely course of events); or he may die instantaneously. Weiss believed that fainting was the cause of death in elderly patients who collapse on getting out of bed after a prolonged period of rest and die instantaneously: "Whenever death is truly instantaneous, it has been my experience that postmortem examination usually disproves the existence of coronary thrombosis, of cerebral vascular accidents or of pulmonary infarcts, which are the erroneous diagnoses usually attached to such sudden and unexpected fatal accidents" (Weiss, 1935*b*).

In earlier chapters I have drawn attention to the fact that when the subject is kept upright in a faint the brain may rapidly develop absolute anoxia. Barcroft (1920) described three kinds of cerebral anoxia—anoxic, anaemic and stagnant—and he argued that the anoxic was the most dangerous. The brain in fact can have only one kind of anoxia—subnormal oxygen tension—though the anoxia may have any one of three origins, as defined by Barcroft, or any combination of the three. Lennox *et al.* (1935 and 1938) showed that the effect was the same whether cerebral oxygen tension was reduced by administering nitrogen or by inducing syncope, that is to say, by anoxic or by stagnant anoxia: with either form consciousness began to be lost when the oxygen saturation of blood in the internal jugular vein fell below 30 per cent and was abolished when it fell below 24 per cent. They noted that cerebral anoxia of anoxic origin was less extreme than that resulting from syncope. It should also be realised that its onset is less rapid.

Anoxic anoxia in its most intense form is seen when a subject breathes an atmosphere from which oxygen is excluded—nitrogen, for example. When this happens, consciousness is lost in about forty seconds. Stagnant anoxia is seen at its worst when the cerebral circulation stops abruptly. Consciousness is then lost in about four seconds. Therefore, the most dangerous and fulminating anoxia is, contrary to Barcroft's suggestion, not that of anoxic, but that of stagnant origin. Moreover, anoxia of stagnant origin, though exceedingly rapid, is more insidious in onset; the striking appearances of the anoxic form are lacking; and the brain may become completely anoxic before the anaesthetist is aware there is anything wrong.

Therefore, if a person is kept upright in a fainting attack, his brain may be in the same danger as if his heart had stopped beating. If he survives the attack there may follow a train of symptoms and signs directly referable to cerebral damage. Depending on the severity and duration of the anoxia and on the location of the damage, the manifestations will range from temporary disturbance of

cerebral function, through degrees of intellectual impairment or dementia, perhaps with few or no physical signs to disclose their organic origin, sometimes with disturbances of posture and of muscle tone and with athetoid movements, to decerebrate rigidity and delayed death.

If the subject falls, fainting is entirely benign: if he is prevented from falling, it is a disorder of extreme danger.

The Fainting Reflex.—In the nineteenth century, fainting was regarded as a form of 'cardiac syncope'—"failure of the heart's action" (Gowers, 1907)—although Newkirk (1896) came near to divining its true nature: "there is extreme dilatation of the arterial vessels generally, and . . . in fatal cases death results, not so much from failure of the heart to act, but because blood is lacking for the heart to act upon . . . The heart is emptied into the relaxed blood vessels."

The 'cardiac syncope' view was not challenged until Lewis investigated fainting in soldiers with 'irritable heart' or 'effort syndrome' during the First World War (Cotton and Lewis, 1918; Lewis, 1932). He concluded that the fall in blood pressure was not entirely due to vagal slowing of the heart, since atropine did not prevent fainting, although it abolished the bradycardia. The chief factor was vasomotor—decreased resistance in the arterioles—and to draw attention to this, Lewis introduced the term 'vasovagal syncope'.

Weiss confirmed Lewis' finding that atropine did not prevent fainting and that the main effect was peripheral, but he thought there was constriction rather than dilatation of the arterioles and that the fall in blood pressure was due to pooling of blood in the veins.

Confirmation of Lewis' concept of arteriolar dilatation was not obtained until the Second World War, when it was accidentally found from plethysmographic tracings recorded by Edholm that forearm blood flow increased during fainting (Barcroft *et al.*, 1944). It was soon shown that the increase in flow was in the muscle vessels and was due, not simply to abolition of vascular tone, but to active vasodilatation in response to impulses transmitted from the vasomotor centre in the sympathetic nerves (Barcroft and Edholm, 1945).

It is now generally accepted that the fall in blood pressure in fainting is due almost entirely to a large decrease in the total peripheral resistance, mainly in muscle vessels. Cardiac output does not, as a rule, change appreciably and may actually increase slightly with the onset of the faint. The mechanism is thought to be the same in all faints, whatever the precipitating factor. The sequence of events appears to be as follows

Prior to the faint, there is a preliminary phase during which there is a progressive decrease in the amount of blood reaching the right side of the heart and therefore in right auricular filling pressure. This is accompanied by a decline in cardiac output. During this phase, blood pressure is fairly well maintained by baroceptor reflexes, though blood pressure may be lower, and heart rate higher, than normal.

The faint itself is then triggered-off. At this, there is a massive parasympathetic discharge from the vasomotor centre. This results in profuse sweating, decrease in heart rate, and active vasodilatation, mainly in muscles. The baroceptor reflexes are overwhelmed, and there is a precipitous fall in blood pressure. At the same time, there is an outpouring of posterior pituitary hormone, to which are attributed the nausea, abdominal discomfort, urge to defaecate, pallor and cutaneous vaso-constriction, and antidiuresis, all of which are associated with fainting.

Sharpey-Schafer (1956) has advanced an attractive hypothesis to explain the phenomena on a reflex basis. He noted that in every kind of faint in which the investigation had been made, decrease in right auricular filling pressure preceded the attack. This is characteristic of haemorrhage. Therefore, all faints, he suggested, are due to haemorrhage or simulated haemorrhage: "Thus standing erect on a hot day is 'bleeding' into the veins of the lower part of the body. The supine posture in late pregnancy causes obstruction of the inferior vena cava by the uterus". And likewise other causes of fainting, such as spinal anaesthesia, prolonged positive-pressure breathing, morphine derivatives, and emotion, simulate haemorrhage, the latter two, perhaps, through splanchnic dilatation.

As a result of the decreasing auricular filling and increasing activity of the heart, the ventricles come to contract on a virtually empty chamber. It is known from animal experiments that when this occurs very high pressure transients may develop, and these, Sharpey-Schafer believes, stimulate afferent nerve endings in a ventricle, probably the left, and trigger-off the reflex. In heart failure, the ventricles are not easily emptied, which may account for the fact that patients in heart failure cannot faint.

Teleological Significance of Fainting.—Most physiological mechanisms can be shown to favour survival of the individual. It is difficult to see what benefit the organism derives from fainting.

Engel (1950*f*) has attempted an explanation. He believes that the basis of fainting is fear. He recalls Darwin's observation in animals that the physiological changes resulting from fear prepare the animal for flight. These changes, Engel finds, resemble some of those seen in fainting, particularly the muscle vasodilatation, which he regards as

a preparation for violent effort. If a man made the natural response of fighting or running away, Engel argues, the increased activity of the muscles and heart would sustain the circulation and he would not faint. But if he restrains himself and stands firm, the blood pressure falls and he faints. Fainting, therefore, in Engel's view, is a harmful consequence of inhibiting the response to a primitive and useful physiological reaction. And he thinks it may not be altogether without value in that by losing consciousness in the face of overwhelming danger the individual is spared psychological trauma, and through the abolition of muscle tone and by falling inert to the ground he may obtain some immunity from attack as do animals that 'freeze' or 'sham dead'.

This hypothesis, however, does not explain the faints that occur in the absence of any pronounced emotion. And if it were correct, the incidence of fainting should bear some relation to the extent of the danger. For example, we would expect fainting in a high proportion of soldiers standing in trenches, waiting to go 'over the top'; but in fact many more will faint on an innoculation parade.

Sharpey-Schafer's observation that all faints are due to haemorrhage or simulated haemorrhage provides a basis for an alternative explanation. It seems to me that if fainting is a reaction to haemorrhage it should be of benefit in haemorrhage; and indeed this might well be so, the decrease in blood pressure diminishing the blood loss. Loss of muscle tone and falling might then be regarded as a secondary adaptation to guard against necrosis of the brain.

APPENDIX B

A CASE OF SPASTIC PARALYSIS FOLLOWING ANAESTHESIA WITH NITROUS OXIDE FOR DENTAL EXTRACTION

Case 17.*—In December, 1953, a girl, nearly nine years old, was given gas in the dental chair for the extraction of teeth. Either then or within a few hours after the operation she developed brain lesions resulting in permanent spastic paralysis and dementia.

Family History.—She was the oldest of three children born of healthy, working-class parents. There was no history in the family of epilepsy, mental disease or other condition relevant to her illness, and the other children were healthy.

Personal History.—She was born in January, 1945. Her infancy was normal, and at the age of 5 she went to a school for normal children. She was a small, weakly child, subject to frequent colds and sore throats, and was shy, dull and a little backward, but not mentally defective. At the age of 7 she was considered to have the intelligence of a child of 5. Intelligence tests made when she was 7 and again when she was 8 gave quotients of 86 and 83 (Terman Merrill).

Past Illnesses.—At the age of 5 she fainted in the street; there was nothing in the attack to suggest epilepsy. At the age of 7 she fainted again, this time at home on a hot summer day. The attack was witnessed by her father, who said that she did not have a convulsion and was only momentarily unconscious. She had measles when she was 7, and also at that age developed a squint, for which glasses were prescribed after she had been examined at an eye hospital.

History of Present Illness.—On the afternoon of December 4, 1953, the child, then in normal health and nearly 9 years old, was taken by her mother to a school dental clinic for the extraction of five teeth. What took place at the clinic was, a month later, made the subject of enquiry by the Chief Dental Officer of the district, who elicited the following information:

The child was anaesthetised by an experienced dental anaesthetist, using nitrous oxide and oxygen delivered from a modern anaesthesia machine of standard make and regularly serviced. Pre-anaesthetic

* For details of this case, I am indebted to Dr. T. R. Malloy, the physician under whose care the patient first came, and to Dr. K. Cameron, who kindly made available to me case notes from the Maudsley Hospital, London.

medication had not been given. Five deciduous teeth were extracted. The administration of the anaesthetic, the operation, and the recovery were said to have been uneventful, and the child was dismissed after about half an hour as a normal case.

This information, however, was to some extent contradicted by that given by the child's mother, when carefully questioned at a later date. She related that her child was the first of six children in the waiting room to be called into the surgery for treatment, but was the last one to leave it; the child was brought out to her by the nurse in attendance not until several minutes after the last of the other children had departed. The delay had caused the mother great anxiety, and when she saw the child she noticed that she was extremely pale, was crying and did not seem to be herself. Nevertheless, they walked home together—a distance of about two hundred yards.

The child continued to cry and would not speak or answer questions. Soon after getting home, while sitting in the parlour chair, she was seen by her father to have what he called a fit. Her legs and arms went suddenly stiff in front of her and began to shake. Her face and body were also involved, the left side, he thought, more than the right. She foamed at the mouth but did not appear to lose consciousness. The fit passed off gradually over a period, he said, of about half an hour.

Thenceforward, her walking was slow, laboured and unsteady. She held her limbs stiffly and rigidly, "as if she was only one year old", the father said. She was quite childish and did not speak, but made singing noises with no words or tune. When asked questions she did not answer but grinned inanely; and when given food she held her cup in her mouth for long periods unless it was taken from her. There were no more fits and she was not at that time incontinent. She vomited once.

During the two days following the dental operation her condition grew worse. She became "dopey" and slept very heavily. A general medical practitioner was sent for but did not make his visit until December 8, four days after the operation, when he sent her at once to hospital.

State on Examination.—*At hospital, she was found to present* a "typical picture of schizophrenic reaction", with extreme catatonia and a grinning, inane expression She appeared to understand simple conversation and gave some indication of answering when her name or age were correctly spoken. She was mute, though not aphonic. There were indications, also, that she was correctly orientated.

Her temperature was 97, her pulse rate 96 and her respirations 20. No abnormality was found in the throat, ears, lungs, cardiovascular system or abdomen.

Central Nervous System.—The pupils were equal in size and reacted normally. Eye movements were normal and there was no nystagmus. The optic discs were normal.

The knee-jerks were bilaterally exaggerated, and the supinator and triceps-jerks absent in the left upper extremity. The plantar reflexes gave doubtful extensor responses.

The cerebrospinal fluid was normal, and an X-ray of skull revealed no abnormality. The Wassermann reaction was negative.

Progress.—On December 11, one week after the operation, she was able to walk but was unsteady. Feeding her was difficult, and she was unresponsive to questioning. Much of the time she lay immobile in bed, wailing, but at other times she walked round the ward and even played with other children. Her posture was awkward and she held her arms upwards and semi-flexed at the elbows. They resisted passive movement, but maintained indefinitely any position enforced upon them. Her gait was more awkward than ataxic, and when she sat down in a chair the movements were stiff and she rolled backwards, drawing up her knees and holding her arms in the position referred to. Her expression was set in an inane grin which seldom relaxed, and saliva dribbled from the corners of her mouth. She was mute but whimpered and made grunting noises. She was able, nevertheless, to pay attention to a story and to draw a house when requested: its outlines were wavy and irregular, but it was not badly proportioned.

Photographs of the child are shown in Fig. 22. The upper photographs, taken a few months before the dental operation, show the child as she was when taken to the dental clinic; the lower one, taken in hospital, shows her condition three weeks later. At this stage she was transferred to the Maudsley Hospital, London.

Her condition on arrival at the hospital was as follows:

She lay in bed in an awkward posture, the legs stiff, the left arm flexed and the right extended. Movements were slow, awkward and stiff. The jaw was fixed, and there was risus sardonicus. The limbs resisted passive movement. She was extremely restless and was constantly making writhing movements. Muscle tone was variable but was always greater on the left side of the body than on the right. There were frequent attacks, lasting one half to two minutes, of increased muscle tone, during which the eyes rolled upwards. There appeared to be comprehension except in the attacks. She was mute, but made grunting or screaming noises. Feeding her was extremely difficult.

The optic discs were pale. The knee jerk on the left side was absent. The left plantar reflex gave an extensor response, the right was equivocal.

In March, 1954, her mental state began to improve; she became more alert, showed more interest in her surroundings and attempted to handle toys. In May she began to attempt to speak single words, and it became clear that her comprehension was at a far higher level than was suggested by her appearance. She was able to indicate most of her needs by gestures. The attacks of increased muscle tone were less frequent and less severe. Contractures were becoming pronounced and needed treatment.

On June 1, 1954, she was discharged from the Maudsley Hospital and sent back to the hospital from which she had come. It was recorded at the Maudsley Hospital that she still needed every nursing attention and help with feeding; that she was occasionally doubly incontinent; that she spent most of the day sitting in a chair, attempting to play with toys; and that the neurological findings were unchanged since admission, except that the attacks of increased muscle tone were less frequent. The suggested diagnosis was demyelinating disease.

Special Investigations.—The following investigations had been made at the *Maudsley Hospital*:

1. Serial electro-encephalograms, made in January, March, April and May, showed much slow (1½–2 c/sec.), bilaterally synchronous activity, seen over both posterior temporal regions; the dominant activity was irregular at 4–7 c/sec., chiefly from the anterior half of the head.
2. X-ray of skull (6/1/54) showed that the floor of the posterior fossa was thinner on the right side than on the left, suggesting possible down-bulging, which might indicate a right-sided cerebellar expanding lesion.
3. Cerebrospinal fluid (11/1/54) was normal.

On readmission to the first hospital, on June 1, 1954, it was noted that, apart from the contractures that had developed, her condition had changed remarkably little during her five months absence. By now she understood simple conversation and answered questions by nodding Her condition remained unaltered until February, 1955, 14 months after the onset of the illness, when she began to have fits in which she went into flexion spasms lasting about a minute. On February 15, 1955, she underwent a neurological examination of which the findings were as follows:

Cranial Nerves.—The ocular fundi were normal, the pupils reacted normally to light, ocular movements were full and there was no trace of nystagmus The mouth was held half open. The palate moved very little. Phonation was very poor and she was mute.

Upper Limbs.—There was a severe, fixed flexion contracture of the



FIG. 22.—*Case* 17 The appearance of the patient before (*above*) and aft (*below*) anaesthesia with nitrous oxide for dental extraction.

left elbow, with partial pronation of the forearm and flexion of the fingers. Movements of the left upper extremity were weak, but in no muscle group was paralysis total. When the right upper extremity was outstretched the forearm tended to be pronated, and there was a suggestion of athetosis. The finger-nose test was performed fairly steadily with the right hand, but with the left there was a moderate intention tremor.

Lower Limbs.—There was abductor spasm with an extreme degree of talipes varus, but very little equinus deformity. (Previous to this examination, manipulations under anaesthesia had been made in an attempt to correct deformities.) As in the upper extremities, paralysis was nowhere complete. Muscle tone was increased, but not greatly so.

Reflexes.—The tendon jerks in the upper extremities were extremely sluggish. The knee-jerks and ankle-jerks were brisk, and there was a fugitive ankle clonus, particularly on the right side. Both plantar responses were extensor. The abdominal reflexes were present.

Abdomen.—Nothing abnormal was discovered on palpation.

Throughout the examination the child co-operated well, and in spite of a persistant inane grin there was no doubt that she understood instantly what was said to her. It was thought that the signs in both lower limbs denoted pyramidal disturbances and that there was no definite evidence of extra-pyramidal rigidity. The postural defect in the hands seemed to be athetoid. There was no evidence that the organic process had progressed in recent months, and there had, in fact, been considerable improvement in motor function since the early stage of her illness.

Tests of Intellectual Capacity.—Tests of intellectual capacity were made in April, 1955, 16 months after the onset of her illness, when she was 10 years and 3 months old. Her physical handicaps prevented an accurate assessment by standard tests, but modified tests indicated a mental age of about 7½ years and placed her in the 'limited ability group'. Retesting confirmed that her intelligence was impaired.

In July, 1955, she was sent home and was later admitted to a residential school for spastic children.

She was re-examined in February, 1957, 3 years and 2 months after the onset of the illness. From the psychiatric point of view she had changed but little since leaving hospital in July, 1955. She had been taught to communicate to some extent by sound, but had a weak nasal voice. She was co-operative and friendly, and in touch with her surroundings. She had no undue emotional lability.

It was thought that, from the neurological point of view, evidence of pyramidal disease, though present, was slight. Most of the disturbances were regarded as a kind of dystonia, and were now

attributed to extra-pyramidal lesions. The cause of the disease was thought to have been some form of localised encephalitis or a demyelinating process, perhaps allied to Schilder's disease.

A fresh neurological examination was made in May, 1959, when she was 14 years old and in the sixth year of her illness. Definite evidence was found of both extra-pyramidal and pyramidal involvement, the latter mainly affecting the left side of her body. She had continued to have epileptic attacks, up to eight a month, and electro-encephalograms suggested that the disturbance arose within the deep, midline structures. The clinical picture was thought to resemble that which may result from thrombosis of the vein of Galen, and this was therefore now suggested as a possible explanation of her illness.

Comment

The diagnosis in this case was difficult. At the onset of the illness the mental manifestations were so pronounced that the minor signs of organic change in the brain were overlooked: the illness masqueraded as acute schizophrenia. When, however, the signs of physical destruction of cerebral tissue were recognised, it became evident that the psychosis was of the organic reaction type. She had, in fact, organic dementia.

The close relationship between the onset of the illness and the administration of nitrous oxide was noted when the child first entered hospital, and subsequently was not lost sight of. But the possibility of the condition being due to anoxia seemed to be negatived by the report of the Chief Dental Officer. It was only later, when, at my request, the child's parents were carefully questioned, that this possibility was re-opened. Meanwhile, other diagnoses had been suggested. Encephalitis, demyelinating disease, Schilder's disease, Wilson's disease, and thrombosis of the vein of Galen were considered at one stage or another; but none of them was altogether satisfactory. The survival of the patient, now in the sixth year of her illness, and the fact that her condition had at first improved and then remained stationary, together with the absence of blindness or deafness, on the one hand, or of any evidence of liver disease, on the other hand, ruled out in turn Schilder's and Wilson's diseases. It seemed, therefore, that her condition would have to be explained on the basis either of some form of localised encephalitis, or of a demyelinating process, perhaps allied to Schilder's disease, or thrombosis of the vein of Galen. The parents' evidence, however, and particularly the mother's, allowed anoxia to be reconsidered as an alternative possibility.

The brain lesions produced by anoxia have been extensively reviewed by Courville (1939*a* and 1953), Hoff *et al.* (1945), Morrison

(1946), Grenell (1946), Meyer (1956 and 1958) and others. It is now *well known that the structures most vulnerable to anoxia* are the neurones of the cerebral cortex, particularly those in the third and fourth layers, the Purkinje cells of the cerebellum, and the cell masses that form the basal ganglia. Less commonly, lesions are to be found also in the subcortical white matter (Steegmann, 1939; Douglas, 1949; Courville, 1955) and Morrison (1946), in experiments with anoxia in animals, produced a pattern of demyelination *that closely resembled that seen in Schilder's disease. The extent to* which these different structures are affected by anoxia varies widely from case to case. In some cases the lesions are almost wholly confined to the cerebral cortex, though Courville (1939*b*) found that the lenticular nucleus was hardly ever spared; in other cases most of the damage is in the basal ganglia. Meyer (1956) has reported a fully investigated case in which the only lesion found was unilateral softening of the globus pallidus.

The signs in the case under review point to lesions in these structures. That the cerebral cortex was involved was suggested by the extensor plantar response; by the mental impairment, which steadily improved during the first few months, a characteristic of anoxia; by the serial electro-encephalograms, which indicated diffuse and bilateral damage, again a characteristic of anoxia; and by the partial, spastic paralysis. Involvement of the extra-pyramidal system was suggested by the plastic rigidity of the lead pipe kind, and by the athetoid movements, signs that might well be accounted for by lesions in the lenticular nucleus. How much of the rigidity in this case was of the spastic or pyramidal type and how much of it was of the plastic or extra-pyramidal type, it was difficult to say; but the

[illegible]

dull, suggested that most of the dystonia was extra-pyramidal. Thus, on pathological grounds the lesions are entirely consistent with a diagnosis of anoxia.

Clinically, also, the manifestations and course of the illness closely resemble those of reported cases in which the anoxic origin of the lesions was not in doubt. I refer particularly to three cases described by Courville (1939*c*, *d* and *e*) and one by Yaskin (1931), *in which the* patients became severely anoxic while anaesthetised with nitrous oxide in the recumbent position, and similar cases in which either respiration or circulation failed during anaesthesia with other agents (Ford *et al.*, 1937; Courville, 1941; Kasin and Parker, 1942; Vernon, 1943; Lucas, 1946; Strohl and Sarver, 1948; Freeman *et al.*, 1954; Polani and Mackeith, 1954; Kral, 1955). In all these cases the patients were left with a degree of dementia and with disturbances of posture

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has arisen from the use of the term 'encephalitis' on no consistent aetiological or pathological basis. Perhaps the same is true also of 'demyelinating' disease. And in cases of anoxia in which the damage falls mainly in the cerebral cortex, there may be little or nothing in the way of physical signs to indicate the organic nature of the resulting psychosis. It seems unlikely that the case I have described, which came to my notice by chance, is unique.

and of muscle tone, similar to those that characterise the present case.

If, then, the cause of the patient's illness was anoxia, there remains to be considered how she came to suffer cerebral anoxia of such severity. In the light of the evidence I have given in the different chapters of this monograph, the most likely explanation would seem to be that she fainted under the gas. She was of poor physique and perhaps prone to faint: she had fainted on two previous occasions. Her pallor when she was returned to her mother at the dental clinic suggests that she had fainted, which would account also for the delayed recovery that seems to have occurred. Nor does the fact that she was able to walk home afterwards rule out the possibility that the cerebral damage had been done actually while she was in the dental chair. For in cases of acute anoxia, temporary recovery, the patient in some cases becoming almost completely normal, followed by relapse, is, as pointed out in Chapter XI, a common feature (Courville, 1936). It is seen even in patients who finally succumb (Caine, 1923; Chabrol, 1923; Lowenberg *et al.*, 1936; Batten and Courville, 1940; Courville, 1941; Dripps *et al*, 1948; Johnson and Kirby, 1949), and a remarkable example is furnished by one of the cases described by Steegmann (1939), briefly referred to in Chapter XI. In that case, the patient, a man aged 20, had respiratory arrest during nitrous oxide anaesthesia for the treatment of a hand injury in a doctor's surgery. Consciousness returned rather slowly and there were involuntary movements of the arms. He was sent to hospital, but the third day he was discharged, his symptoms being thought to be hysterical Later he lapsed into coma and died. The brain lesions found at necropsy were characteristic of anoxia.

But in the case under review there is another possible explanation If we suppose that the child had fainted in the dental chair, which offers the best explanation of her pallor and of the delay at the dental clinic, then the attack witnessed by the father while she was in the parlour chair may also have been a faint. Once a person has fainted the tendency to faint again if placed upright may persist for hours; and the father's description of the attack is consistent with its having been a faint. If this was in fact the case, then it may well have been during the second attack that the main damage was done. The child did not fall in this attack and was left sitting up; and there is little doubt that after it her condition became decidedly worse.

If either of these explanations is correct and the lesions were in fact due to anoxia, then the question arises whether there are not similar cases masquerading as psychosis, demyelinating disease or some form of unexplained 'encephalitis'. Yaskin (1931), and more recently Walshe (1955), have drawn attention to the confusion that

made to take fluids or food. Her temperature was 100 and her pulse rate 120. Fever continued for three days.

On physical examination the only abnormality found was a doubtful extensor plantar response on the left side. The cerebrospinal fluid was not examined.

Laboratory and other special investigations, including the Wassermann reaction and an x-ray photograph of skull, were negative.

Progress.—Four days after the dental operation she was "making slow improvement". On April 25, nine days after the operation, she was "more wide awake". There had been no fits. Next day she was considered to have made a complete recovery and was sent home. The suggested diagnosis was post-epileptic confusional state.

On May 21, 1957, she was readmitted to hospital for further dental treatment under anaesthesia. She was examined by a neurologist (Dr. P. K. Robinson) and the only abnormal physical sign was slight inequality in the abdominal reflexes. He confirmed that for about twelve months she had been having minor attacks of an epileptic kind; and on evidence given by the mother, who said that since the dental operation the child was less bright, had a tendency to get confused and muddled, and was unable to concentrate or read except for short intervals, he thought there might have been certain changes due to anoxia during the dental operation.

On May 24, 1957, a second dental operation was performed, and I myself gave the anaesthetic. The patient was supine. After preanaesthetic medication with scopolamine gr. 1/150 (0·4 mg.), anaesthesia was induced with thiopentone 200 mg. and suxamethonium 40 mg., and was continued with 80 per cent nitrous oxide and 20 per cent oxygen given through a cuffed endotracheal tube passed through the nose.

Throughout the operation, which lasted 40 minutes, anaesthesia was uneventful. But just as the operation was finished and before the anaesthetic was withdrawn, she had a typical attack of grand mal epilepsy. The moment it started, her lungs were inflated with oxygen. Her colour remained normal, and her pulse strong; at no time was there either lack of oxygen or hypotension.

The attack was followed by a period of unconsciousness and stupor lasting nearly an hour, after which she became fully conscious, but complained of headache. Convalescence was normal and no further epileptic attack was seen.

I am indebted to Dr. Denis Hill for the following report on electroencephalograms taken on May 28, 1957, six weeks after the first and four days after the second dental operation:

"Alpha activity at 8 c/sec. is evident in the postcentral areas, but shows poor symmetry and is disturbed on both sides by slow

APPENDIX C

A CASE OF DELAYED RECOVERY FOLLOWING ANAESTHESIA WITH NITROUS OXIDE FOR DENTAL EXTRACTION

Case 18.—In April, 1957, a girl, aged 14 and subject to attacks of petit mal, was given gas in the dental chair for the extraction of two teeth. She had syncope under the gas, and normal consciousness was not regained for several days. Electro-encephalograms taken six weeks later showed abnormalities consistent with anoxic brain damage.

Personal History.—The patient was born in September, 1942. Her childhood had been healthy except that in recent months she had been having attacks of petit mal, for which she had been given phenobarbitone gr. ½ (30 mg.) twice daily. There had been no grand mal attack. (Her brother was an epileptic.) At the age of 11 she had been given nitrous oxide for dental extraction without ill effect.

History of Present Illness.—On the morning of April 16, 1957, she was given gas by her doctor at a dentist's surgery. She took the anaesthetic well and two teeth were quickly extracted, after which she became cyanosed and rigid, and then pale. The pallor was extreme, the pupils were dilated and her appearance was deathly. There was sweating, twitching of muscles and some convulsive movements. Breathing became very shallow and almost stopped, with long pauses between breaths. She was kept upright, the jaw was held forward and oxygen was given. A little later the chair was tilted backwards into the horizontal position.

She remained unconscious, though every few minutes she moved, and for a moment it looked as if consciousness was returning. After about two and a half hours she was still completely out of contact with her surroundings. She was supported to a taxi and was taken home and put to bed.

Her doctor thought there was a "large hysterical element about her behaviour after the gas". There were occasional spasmodic movements of the upper extremities, but no generalised convulsions. On the evening of the next day, being still unconscious, she was sent to hospital.

State on Examination.—On admission to hospital she was "semi-conscious". Her eyes were open but she would not obey commands or co-operate in any way. She resisted examination and could not be

APPENDIX D

THE QUESTIONARY TO DENTISTS

The form in which the questionary to dentists was sent was as follows:

21st April, 1955.

Dear......

I am very interested in the problem of general anaesthesia (gas, etc.) for patients in the dental chair. I am writing to a number of dental surgeons, selected at random up and down the country, asking for their views. I should be most grateful if you would be so kind as to give me your opinion by answering the questions set out below.

Yours sincerely,

Anaesthetist,
St. Thomas's Hospital,
London.

1. Do you sometimes extract teeth from patients under general anaesthesia in the chair? ....
2. If so, please indicate approximately in what percentage of patients undergoing general anaesthesia each of the following anaesthetics is used:
   (*i*) *Nitrous oxide without oxygen* ....
   (*ii*) *Nitrous oxide with oxygen* ....
   (*iii*) *Nitrous oxide, oxygen and trilene* ....
   (*iv*) *Pentothal, nitrous oxide and oxygen* ....
   (*v*) *Pentothal alone* ....
   (*vi*) *Ethylchloride* ....
   (*vii*) *Vinesthene* ....
   (*viii*) *Others (if so, which)* ....
3. Solely from the point of view of the operating conditions and length of time that it gives you, do you find the anaesthesia always completely satisfactory? ....
4. If not, do you find it:

(*i*) *Slightly unsatisfactory*	*Occasionally*	......	*Please say YES*
	Often	......	*or NO*
(*ii*) *Very unsatisfactory*	*Occasionally*	......	*to each of*
	Often	......	*these.*

wave activity predominantly at 4–6 c/sec. This activity is larger on the left side than the right and is widespread, extending into the frontal areas and blocking poorly on visual attention. Overbreathing increases the slow wave activity, again particularly on the left side.

"This EEG. shows no focal abnormality, no spike discharges and no evidence of epileptic activity. The record is abnormal for a girl of 14 by reason of the excess of slow activity which is lateralised predominantly to the left side. At this age, in the absence of focal abnormality, it cannot be regarded as evidence for a macroscopic lesion. The EEG. is however compatible with a history of a period of significant anoxia six weeks previously".

Comment

Whatever may have been the nature of the attack during the first dental operation, the patient undoubtedly had syncope of one kind or another; and since she was kept upright, this would have resulted in severe cerebral anoxia. An epileptic seizure might exacerbate the hypoxia inherent in nitrous-oxide anaesthesia. Therefore, if the attack was epileptic, the syncope may have been due to anoxic heart failure. However, from the description given by the dentist and anaesthetist, it seemed that cyanosis was less striking than pallor, and that the convulsive movements came on only after the patient's appearance had become death-like. Moreover, induction had been brief and without difficulty. Therefore, the most probable explanation would seem to be that the patient fainted under the gas.

If the abnormalities in the electro-encephalograms taken six weeks after the anoxic episode can be accepted as evidence of permanent neuronal damage in the cerebral cortex, this case illustrates the fact that recovery from anoxia may appear on clinical evidence to be complete in spite of permanent cerebral damage.

APPENDIX E

THE NUMBER OF ADMINISTRATIONS OF GENERAL ANAESTHESIA GIVEN ANNUALLY IN ENGLAND AND WALES

Figures given in this appendix are for England and Wales; there are no data for other parts of the United Kingdom. Those relating to ambulatory dental patients are for the year 1952. For assistance in estimating the total number of administrations of general anaesthesia in ambulatory dental patients, I am indebted to Dr. W. G. Senior, Chief Dental Officer of the Ministry of Health.

Patients undergoing general anaesthesia can be divided into two classes: ambulatory and non-ambulatory. The ambulatory class can be divided into dental and non-dental cases.

1. Ambulatory Patients

(*a*) *Dental Cases.*—There are five separate fields from which data are required in order to arrive at the annual total of administrations in dental cases:

School Dental Service
General Dental Service
Local Authority Maternity and Child Welfare Services
Hospitals (including dental teaching hospitals)
Private Practice

The number of administrations in the School Dental Service is given in the Report of the Chief Medical Officer of the Ministry of Education (1954). For the year 1952 the total was 603,421.

The number given in the General Dental Service is less readily obtained. A first approximation can be computed from the number of estimates that included items for general anaesthesia in a sample of estimates approved for payment by the Dental Estimates Board. This number is expressed as a ratio of the population. In 1952, the ratio was 23 per thousand (Chief Medical Officer, Ministry of Health, 1953). Since in that year the population of England and Wales was 44,166,000 (Registrar-General, 1953*c*), it follows that the number of estimates containing items for general anaesthesia was about 1,016,000. This total, however, does not include estimates for emergency treatments, which the Chief Dental Officer, after referring to unpublished data, suggested in a personal communication

5. Do you have any anaesthetic failures? ....
6. Have you ever known a patient who did not immediately regain consciousness after gas but remained unconscious or stuporous for half an hour or more? ....
7. Your comments (if any) ....

Questions 1 and 6 have been dealt with in the text; Questions 2 to 5 will be considered here.

Question 2 was answered by 279 dentists. As expected, unsupplemented nitrous oxide was by far the most commonly used anaesthetic. In the practices of about two-thirds of the dentists, it was used in more than 90 per cent of patients undergoing general anaesthesia; and in the practices of most of the remaining third, it was used in a high proportion of cases. In only one practice was it not used. Nitrous oxide supplemented with trichloroethylene appeared to come next in order of popularity. The other anaesthetics, alone or as supplements to nitrous oxide, were used in only a small proportion of cases.

Questions 3, 4 and 5, which concerned the quality of anaesthesia, were answered by 280 dentists. Their opinions are summarised in Table VI.

TABLE VI

THE QUALITY OF ANAESTHESIA: OPINIONS OF 280 DENTISTS ANSWERING QUESTIONS 3, 4 AND 5

Question		*Number of Dentists Answering Yes*	*Per cent*
3. Is anaesthesia always completely satisfactory?		39	14
4. (i) Is anaesthesia slightly unsatisfactory?	Occasionally	186	66
	Often	19	7
4. (ii) Is anaesthesia very unsatisfactory?	Occasionally	92	33
	Often	3	1
5. Do you have anaesthetic failures?		151	54

therefore, that administrations to ambulatory patients, all types of operation included, greatly outnumber those given to non-ambulatory patients.

The Anaesthetics Used in Ambulatory Dental Patients

That unsupplemented nitrous oxide is far the most commonly used anaesthetic in ambulatory dental patients is suggested by evidence from three different sources:

(*a*) Replies to Question 2 in the questionary to dentists (Appendix D).

(*b*) Information given by Mr. W. R. Young, Chief Dental Officer of the London County Council. In 1954, nearly 44,000 children were given general anaesthesia in the London County Council School Dental Service. In 97·6 per cent of the cases the anaesthetic was nitrous oxide.

(*c*) Information given by Kemp (1955) in a personal communication. In 2,886 consecutive patients anaesthetised in 1955 at the National Dental Hospital, London, unsupplemented nitrous oxide was used in 75 per cent, and nitrous oxide supplemented with trichloroethylene in a further 19 per cent.

Probably in at least three quarters of the ambulatory dental patients undergoing general anaesthesia in the United Kingdom, the anaesthetic used is unsupplemented nitrous oxide, and in most of the remainder it is nitrous oxide supplemented with trichloroethylene.

amounted to about 510,000. The number of estimates containing items for general anaesthesia was therefore about 1,526,000. However, the number of administrations of anaesthesia is somewhat higher than this, since some estimates include more than one administration. Making allowance for this, the Chief Dental Officer suggests a total for the General Dental Service of 1,600,000 administrations, about 600,000 of which, he states, were in children under 15 years of age.

There are no published data for the Local Authority Maternity and Child Welfare Services, hospitals or private practice. Estimating the administrations in these services at about 300,000, the Chief Dental Officer arrives at a grand total for the year for the whole field of dental practice in England and Wales of about two and a half million administrations, about half the patients being children under 15. It should be noted that these figures refer to administrations, not patients: many patients undergo anaesthesia more than once in the year.

(*b*) *Non-dental Cases.*—There are no data for the number of administrations of general anaesthesia given annually to ambulatory patients for minor operations other than dental. The number is undoubtedly large.

2. Non-Ambulatory Patients

The only data on the number of administrations given to non-ambulatory patients (those admitted to hospitals) appear to be those given in the report on an inquiry concerning explosions in operating theatres made in 1954 by the Chief Medical Officer of the Ministry of Health (1955) This report shows that, in one week of that year, about 56,000 operations were performed in the National Health Service hospitals of England and Wales. In more than 12,000 of these operations, however, the patient was given local, regional, epidural or spinal anaesthesia. Therefore, although these forms of anaesthesia are sometimes combined with general anaesthesia, the number of administrations of general anaesthesia would have been less than 56,000. Moreover, a further deduction would have to be made for an unspecified number, included in the total, in which the patients were ambulatory. If we accept 50,000 as the number of administrations of general anaesthesia to non-ambulatory patients—probably too high an estimate—and multiply by 51 (allowing one week for public holidays), we reach, as a rough approximation, an estimate of about two and a half million for the administrations given to non-ambulatory patients during the year

This, it will be noted, is the same figure as the estimate arrived at for ambulatory dental patients alone. It seems fairly certain

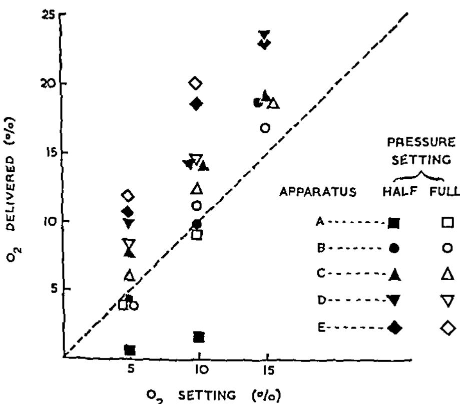


FIG. 23.—Calibration of five dental anaesthesia machines. The broken line represents conformity between the oxygen setting and the amount delivered.

per cent; with the control set at 10 per cent, the amounts varied between 1·7 per cent and 20·1 per cent; and with the control set at 15 per cent, they varied between 18·8 per cent and 23·0 per cent.

COMMENT

The wide discrepancies between the oxygen settings and the amounts of oxygen delivered make the provision of a graduated oxygen scale unwarrantable.

APPENDIX F

CALIBRATION OF DENTAL ANAESTHESIA MACHINES

Dental anaesthesia machines have two controls. The first regulates the amount of oxygen in the mixture. The second (referred to as the 'pressure' control) regulates the flowrate of the mixed gases.

Considerable reliance is placed by anaesthetists on the accuracy of the oxygen control. The oxygen scale is graduated in steps of 1 up to 10 per cent oxygen, and then in steps of 5 up to 20 per cent oxygen, after which there is no further marking except for 100 per cent oxygen. The method most commonly used is to give no oxygen until anaesthesia is established, when the oxygen control is set at some point between 5 per cent and 10 per cent oxygen. Very often the control is placed first at 5 per cent and then advanced to 7 per cent oxygen. The percentage of oxygen delivered by the machine should not only correspond to the marking on the scale but should also remain constant at all 'pressure' settings.

In this investigation, the oxygen calibration of five machines (Apparatus A-E) was tested. They were of standard design, regularly serviced and in regular use, two at St. Thomas's Hospital, and three at St. Bartholomew's Hospital. For analysis of the gas mixtures delivered by Apparatus A, I am indebted to the Research and Development Department of the British Oxygen Company, who used a mass spectrometer. For the other machines a Cambridge Para-Magnetic Oxygen Meter was used. I am indebted to Dr. D. V. Bates for permission to use this instrument and for his assistance with the analyses The calibration of the instrument had been checked against Haldane analyses and the maximal likely error in the range of oxygen percentage that was examined was 0 3 per cent. The analyses were interspersed by regular calibration checks, and when these showed that a slight drift had occurred the results were corrected accordingly. Each apparatus was tested with the 'pressure' control set at 'half pressure' and again at 'full pressure', and with oxygen settings of 5 per cent and 10 per cent Some readings were made also with an oxygen setting of 15 per cent.

Results

The results are shown graphically in Fig. 23. With the oxygen control set at the 5 per cent mark, the amounts of oxygen actually delivered by the apparatuses varied between 0 6 per cent and 11·9

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